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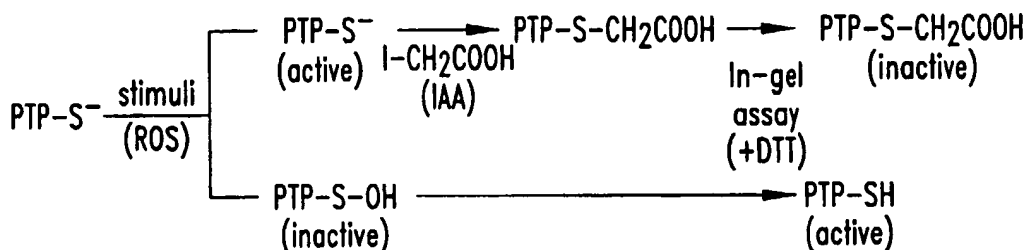
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(54) Title: REVERSIBLE OXIDATION OF PROTEIN TYROSINE PHOSPHATASES



(57) Abstract: The invention relates to a method of identifying any protein tyrosine phosphatase (PTP) that undergoes reversible modification of PTP active site invariant cysteine within a cell, such that the phosphatase is transiently protected from irreversible active site invariant cysteine-directed PTP inactivating agents. Methods related to regulation of PTPs by reactive oxygen species (ROS) in a cellular environment are provided. Multiple PTPs are shown to be reversibly oxidized and inactivated following treatment of cells with H<sub>2</sub>O<sub>2</sub> or with physiological stimuli that promote ROS formation, and inhibition of PTP function is shown to contribute to ROS-induced mitogenesis. Transient oxidation of the PTP catalytic site invariant cysteine is exploited in methods to identify which of multiple candidate PTPs are components of a given biological signal transduction pathway, without a requirement for first specifically purifying any particular candidate PTP.

## REVERSIBLE OXIDATION OF PROTEIN TYROSINE PHOSPHATASES

## CROSS-REFERENCE TO RELATED APPLICATION

5                   This application claims the benefit of U.S. Provisional Patent Application No. 60/356,810 filed February 13, 2002, which is incorporated herein by reference in its entirety.

## STATEMENT OF GOVERNMENT INTEREST

10                   The United States government may have certain rights in this invention under grant number R01-GM55989 from the National Institutes of Health.

## BACKGROUND OF THE INVENTION

15                   The present invention relates generally to compositions and methods useful for treating conditions associated with defects in cell proliferation, cell differentiation and/or cell survival. The invention is more particularly related to identifying protein tyrosine phosphatases (PTPs) that are reversibly modified, including PTPs that are reversibly oxidized components of inducible biological signaling pathways.

20                   Reversible protein tyrosine phosphorylation, coordinated by the action of protein tyrosine kinases (PTKs) that phosphorylate certain tyrosine residues in polypeptides, and protein tyrosine phosphatases (PTPs) that dephosphorylate certain phosphotyrosine residues, is a key mechanism in regulating many cellular activities. It is becoming apparent that the diversity and complexity of the PTPs and PTKs are  
25 comparable, and that PTPs are equally important in delivering both positive and negative signals for proper function of cellular machinery. Regulated tyrosine phosphorylation contributes to specific pathways for biological signal transduction, including those associated with cell division, cell survival, apoptosis, proliferation and differentiation. Defects and/or malfunctions in these pathways may underlie certain  
30 disease conditions for which effective means for intervention remain elusive, including for example, malignancy, autoimmune disorders, diabetes, obesity and infection.

The protein tyrosine phosphatase (PTP) family of enzymes consists of more than 500 structurally diverse proteins that have in common the highly conserved 250 amino acid PTP catalytic domain, but which display considerable variation in their non-catalytic segments (Charbonneau and Tonks, 1992 *Annu. Rev. Cell Biol.* 8:463-493; Tonks, 1993 *Semin. Cell Biol.* 4:373-453). This structural diversity presumably reflects the diversity of physiological roles of individual PTP family members, which in certain cases have been demonstrated to have specific functions in growth, development and differentiation (Desai et al., 1996 *Cell* 84:599-609; Kishihara et al., 1993 *Cell* 74:143-156; Perkins et al., 1992 *Cell* 70:225-236; Pingel and Thomas, 1989 *Cell* 58:1055-1065; Schultz et al., 1993 *Cell* 73:1445-1454; Fukada et al., 1999 *Growth Factors* 17:81-91; Gutch et al., 1998 *Genes Dev.* 12:571-85; Marengere et al., 1996 *Science* 272:1170-73). PTPs participate in a variety of physiologic functions, providing a number of opportunities for therapeutic intervention in physiologic processes through alteration (*i.e.*, a statistically significant increase or decrease) or modulation (*e.g.*, up-regulation or down-regulation) of PTP activity. For example, therapeutic inhibition of PTPs such as PTP1B in the insulin signaling pathway may serve to augment insulin action, thereby ameliorating the state of insulin resistance common in Type II diabetes patients.

Although recent studies have also generated considerable information regarding the structure, expression and regulation of PTPs, the nature of many tyrosine phosphorylated substrates through which the PTPs exert their effects remains to be determined. Studies with a limited number of synthetic phosphopeptide substrates have demonstrated some differences in the substrate selectivities of different PTPs (Cho et al., 1993 *Protein Sci.* 2: 977-984; Dechert et al., 1995 *Eur. J. Biochem.* 231:673-681). Analyses of PTP-mediated dephosphorylation of PTP substrates suggest that catalytic activity may be favored by the presence of certain amino acid residues at specific positions in the substrate polypeptide relative to the phosphorylated tyrosine residue (Salmeen et al., 2000 *Molecular Cell* 6:1401; Myers et al., 2001 *J. Biol. Chem.* 276:47771; Myers et al., 1997 *Proc. Natl. Acad. Sci. USA* 94:9052; Ruzzene et al., 1993 *Eur. J. Biochem.* 211:289-295; Zhang et al., 1994 *Biochemistry* 33:2285-2290). Thus,

although the physiological relevance of the substrates used in these studies is unclear, PTPs display a certain level of substrate selectivity *in vitro*.

The PTP family of enzymes contains a common evolutionarily conserved segment of approximately 250 amino acids known as the PTP catalytic domain. Within this conserved domain is a unique signature sequence motif,

[I/V]HCXAGXXR[S/T]G

SEQ ID NO:98,

that is invariant among all PTPs. The cysteine residue in this motif is invariant in members of the family and is known to be essential for catalysis of the phosphotyrosine dephosphorylation reaction. It functions as a nucleophile to attack the phosphate moiety present on a phosphotyrosine residue of the incoming substrate. If the cysteine residue is altered by site-directed mutagenesis to serine (*e.g.*, in cysteine-to-serine or “CS” mutants) or alanine (*e.g.*, cysteine-to-alanine or “CA” mutants), the resulting PTP is catalytically deficient but retains the ability to complex with, or bind, its substrate, at least *in vitro*.

CS mutants of certain PTP family members, for example, MKP-1 (Sun et al., 1993 *Cell* 75:487), may effectively bind phosphotyrosyl polypeptide substrates *in vitro* to form stable enzyme-substrate complexes, thereby functioning as “substrate trapping” mutant PTPs. Such complexes can be isolated from cells in which both the mutant PTP and the phosphotyrosyl polypeptide substrates are present. According to non-limiting theory, expression of such a CS mutant PTP can thus antagonize the normal function of the corresponding wildtype PTP (and potentially other PTPs and/or other components of a PTP signaling pathway) via a mechanism whereby the CS mutant binds to and sequesters the substrate, precluding substrate interaction with catalytically active, wildtype enzyme (*e.g.*, Sun et al., 1993).

CS mutants of certain other PTP family members, however, may bind phosphotyrosyl polypeptide substrates and form complexes that exist transiently and are not stable when the CS mutant is expressed in cells, *i.e.*, *in vivo*. The CS mutant of PTP1B is an example of such a PTP. Catalytically deficient mutants of such enzymes that are capable of forming stable complexes with phosphotyrosyl polypeptide substrates



may be derived by mutating a wildtype protein tyrosine phosphatase catalytic domain invariant aspartate residue and replacing it with an amino acid that does not cause significant alteration of the  $K_m$  of the enzyme but that results in a reduction in  $K_{cat}$ , as disclosed, for example, in U.S. Patent Nos. 5,912,138 and 5,951,979, in U.S. Application No. 09/323,426 and in PCT/US97/13016. For instance, mutation of Asp 5 181 in PTP1B to alanine to create the aspartate-to-alanine (D to A or DA) mutant PTP1B-D181A results in a PTP1B "substrate trapping" mutant enzyme that forms a stable complex with its phosphotyrosyl polypeptide substrate (e.g., Flint et al., 1997 *Proc. Nat. Acad. Sci. USA* 94:1680). Substrates of other PTPs can be identified using a 10 similar substrate trapping approach, for example substrates of the PTP family members PTP-PEST (Garton et al., 1996 *J. Mol. Cell. Biol.* 16:6408), TCPTP (Tiganis et al., 1998 *Mol. Cell Biol.* 18:1622), PTP-HSCF (Spencer et al., 1997 *J. Cell Biol.* 138:845) and PTP-H1 (Zhang et al., 1999 *J. Biol. Chem.* 274:17806).

Mitogen-activated protein kinases (MAP-kinases) are present as 15 components of conserved cellular signal transduction pathways that have a variety of conserved members. MAP-kinases are activated by phosphorylation at a dual phosphorylation motif with the sequence Thr-X-Tyr (by MAP-kinase kinases), in which phosphorylation at the tyrosine and threonine residues is required for activity. Activated MAP-kinases phosphorylate several transduction targets, including 20 transcription factors. Inactivation of MAP-kinases is mediated by dephosphorylation at this site by dual-specificity phosphatases referred to as MAP-kinase phosphatases. In higher eukaryotes, the physiological role of MAP-kinase signaling has been correlated with cellular events such as proliferation, oncogenesis, development and differentiation. Accordingly, the ability to regulate signal transduction via these pathways could lead to 25 the development of treatments and preventive therapies for human diseases associated with MAP-kinase signaling, such as cancer.

Dual-specificity protein tyrosine phosphatases (dual-specificity phosphatases) are phosphatases that dephosphorylate both phosphotyrosine and phosphothreonine/serine residues (Walton et al., *Ann. Rev. Biochem.* 62:101-120, 30 1993). Several dual-specificity phosphatases that inactivate a MAP-kinase have been identified, including MKP-1 (WO 97/00315; Keyse and Emslie, *Nature* 59:644-647,

1992), MKP-2 (WO97/00315), MKP-4, MKP-5, MKP-7, Hb5 (WO 97/06245), PAC1 (Ward et al., *Nature* 367:651-654, 1994), HVH2 (Guan and Butch, *J. Biol. Chem.* 270:7197-7203, 1995) and PYST1 (Groom et al., *EMBO J.* 15:3621-3632, 1996). Expression of certain dual-specificity phosphatases is induced by stress or mitogens, but  
5 others appear to be expressed constitutively in specific cell types. The regulation of dual-specificity phosphatase expression and activity is critical for control of MAP-kinase mediated cellular functions, including cell proliferation, cell differentiation and cell survival. For example, dual-specificity phosphatases may function as negative regulators of cell proliferation. It is likely that there are many such dual-specificity  
10 phosphatases, with varying specificity with regard to cell type or activation. However, the regulation of dual specificity phosphatases remains poorly understood and only a relatively small number of dual-specificity phosphatases have been identified.

Currently, desirable goals for determining the molecular mechanisms that govern PTP-mediated cellular events include, *inter alia*, determination of PTP  
15 interacting molecules, substrates and binding partners, and identification of agents that regulate PTP activities. In some situations, however, current approaches may lead to an understanding of certain aspects of the regulation of tyrosine phosphorylation by PTPs, but still may not provide strategies to control specific tyrosine phosphorylation and/or dephosphorylation events within a cell. Accordingly, there is a need in the art for an  
20 improved ability to manipulate phosphotyrosine signaling, including intervention in the regulation of PTPs. An increased understanding of PTP regulation may facilitate the development of methods for modulating the activity of proteins involved in phosphotyrosine signaling pathways, and for treating conditions associated with such pathways.

25 Hence, and as also noted above, over the last fifteen years it has been established that the Protein Tyrosine Phosphatases (PTPs) are a large, structurally diverse family of receptor-like and non-transmembrane enzymes, which exhibit exquisite substrate specificity *in vivo* and are critical regulators of a wide array of cellular signaling pathways (Andersen et al., 2001 *Mol. Cell. Biol.* 21:7117; Tonks and  
30 Neel, 2001 *Curr. Opin. Cell Biol.* 13:182). An important area of investigation in the field remains the characterization of mechanisms by which the activity of the PTPs

themselves may be regulated *in vivo*. Recently, the proposal that certain PTPs may be susceptible to oxidation and inactivation has introduced an additional tier of complexity to the regulation of this family of enzymes.

It is now apparent that reactive oxygen species (ROS) are not merely a  
5 harmful by-product of life in an aerobic environment. The importance of ROS in phagocytic cells, such as neutrophils, is well documented. Various stimuli lead to the assembly of a multi-component NADPH oxidase complex, which mediates a process known as the respiratory burst (DeLeo et al., 1996 *J. Leukoc. Biol.* 60:677). NADPH oxidase catalyses transfer of one electron from NADPH to molecular oxygen to  
10 generate superoxide anions, which in turn may yield hydrogen peroxide, either via protonation of superoxide or through the action of superoxide dismutase (Thelen et al., 1993 *Physiol. Rev.* 73:797). The large quantities of such ROS produced in phagocytic cells have been implicated as microbicidal agents and in certain pathological situations can result in host cell damage (Smith et al., 1991 *Blood* 77:673). However, many  
15 recent studies have revealed that the production of ROS is tightly regulated, engendering the concept that, at lower levels than those generated for a microbicidal function, ROS may also function in propagating a signaling response to extracellular stimuli (Finkel, 1998 *Curr. Opin. Cell Biol.* 10:248; Finkel, 2000 *FEBS Lett.* 476:52). Thus, in a manner analogous to reversible protein phosphorylation, the reversible  
20 oxidation of target proteins in a cell may regulate the function of those proteins in response to various agonists and thus elicit a cellular response to stimulation (Finkel, 1998).

Several lines of investigation have implicated ROS in the regulation of mitogenic signaling in mammalian cells (Adler et al., 1999 *Oncogene* 18:6104;  
25 Brummel et al., 1996 *J. Biol. Chem.* 271:1455-61; Chen et al., 1995 *J. Biol. Chem.* 270:28499; Sundaresan et al., 1995 *Science* 270:296). Mild oxidation can yield a stable sulfenic acid modification of cysteine residues (Cys-SOH) in selected proteins, including a variety of enzymes and transcription factors, which has the potential to regulate the function of those proteins (Claiborne et al., 1999 *Biochemistry* 38:15407).  
30 In order to understand the role of ROS and redox regulation in the control of signal transduction, it is particularly important to identify the targets of reversible oxidation *in*

*vivo*. In this context, attention has been drawn to the PTPs, which together with the PTKs are responsible for maintaining a normal tyrosine phosphorylation status *in vivo*. As described above, the PTPs are characterized by a signature motif, I/V-H-C-X-X-G-X-X-R-S/T, which forms the base of the active site cleft and contains an invariant Cys residue (Barford et al., 1995 *Nat. Struct. Biol.* 2:1043). The catalytic mechanism involves a two-step process, commencing with nucleophilic attack by the S $\gamma$  atom of the catalytic Cys on the phosphorus atom of the phosphotyrosyl substrate, resulting in formation of a phospho-Cys intermediate. In the second step the transient phosphoenzyme intermediate is hydrolyzed by an activated water molecule (Barford et al., 1995). Due to the unusual environment of the PTP active site, the pK $\alpha$  of the sulfhydryl group of this Cys residue is extremely low (~5.4 in PTP1B, (Lohse et al., 1997 *Biochemistry* 36:4568) and ~4.7 in YOP, (Zhang et al., 1993 *Biochemistry* 32:9340)) compared to the typical pK $\alpha$  for Cys (~8.5), which favors its function as a nucleophile but renders it susceptible to oxidation. It has now been shown *in vitro* that treatment with H<sub>2</sub>O<sub>2</sub> of various PTPs (Lee et al., 1998 *J. Biol. Chem.* 273:15366), dual specificity phosphatases (Denu et al., 1998 *Biochemistry* 37:5633) and low molecular weight PTPs (Caselli et al., 1998 *J. Biol. Chem.* 273:32554) leads to oxidation of the active site Cys to sulfenic acid. Such oxidation results in inhibition of activity, because the modified Cys can no longer function as a phosphate acceptor in the first step of the PTP-catalyzed reaction.

Oxidation of Cys to sulfenic acid is reversible (Claiborne et al., 1999 *Biochemistry* 38:15407) and thus has the potential to form the basis of a mechanism for reversible regulation of PTP activity. In contrast, oxidation by the addition of 2 (sulfinic acid) or 3 (sulfonic acid) oxygens to the active site Cys is irreversible. Interestingly, glutathionylation of the sulfenic acid form of PTP1B has been reported (Barrett et al., 1999 *Biochemistry* 38:6699) and proposed as a mechanism to protect against further, irreversible oxidation and as an important step in the reverse, reduction mechanism. Stimulation of A431 cells with EGF was also shown to lead to the production of H<sub>2</sub>O<sub>2</sub> and concomitant inhibition of PTP1B (Bae et al., 1997 *J. Biol. Chem.* 272:217). Increased production of intracellular oxidants may contribute to enhanced, tyrosine phosphorylation-dependent signaling, for example in response to

growth factors (Bae et al., 1997; Bae et al., 2000 *J. Biol. Chem.* 275:10527; Sundaresan et al., 1995 *Science* 270:296), by transiently suppressing the enzymatic activity of members of the PTP family, thereby promoting a burst of PTK activity (Finkel, 1998; 2000).

5                   However, it is unclear how broadly this phenomenon may apply across the PTP family, and methods have not previously been available for assessing potential reversible oxidation in a broad range of PTPs in a cellular context, *i.e.*, within a living cell, or *in vivo*. In particular, there is a need for a method by which one or more oxidized/inactivated PTPs in a cell could be distinguished from reduced/activated PTPs  
10 in the cell, and in a manner which need not be specific for a particular PTP, or which need not require that each PTP being investigated be highly purified (*e.g.*, specifically immunoprecipitated) or recombinantly cloned and expressed. An increased understanding of PTP regulation in biological signal transduction, including via inducible signaling pathways triggered by biological stimuli, may facilitate the  
15 development of methods for modulating the activity of proteins involved in PTK/PTP cascades, and for treating conditions associated with such cascades. The present invention fulfills these needs and further provides other related advantages.

#### SUMMARY OF THE INVENTION

20                   It is an aspect of the present invention to provide a method for identifying a protein tyrosine phosphatase that is reversibly oxidized in a cell, comprising contacting a biological sample comprising a cell that comprises at least one protein tyrosine phosphatase with a stimulus under conditions and for a time sufficient  
25 to induce reversible oxidation of at least one protein tyrosine phosphatase in the cell; isolating anaerobically the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; determining under reducing conditions a level of dephosphorylation of a detectably labeled protein tyrosine  
30 phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and

therefrom identifying a protein tyrosine phosphatase that is reversibly oxidized in a cell. In one embodiment, the invention provides a method for identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is reversibly oxidized in a cell, comprising contacting a biological sample comprising a cell that comprises SHP-2 with a stimulus  
5 under conditions and for a time sufficient to induce reversible oxidation of SHP-2 in the cell; isolating anaerobically SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; determining under reducing conditions a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2 comprises a polypeptide  
10 comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, and wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is reversibly oxidized in a cell. In another embodiment, the invention provides a method for identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is reversibly oxidized in a cell, comprising  
15 contacting a biological sample comprising a cell that comprises PTP1B with a stimulus under conditions and for a time sufficient to induce reversible oxidation of PTP1B in the cell; isolating anaerobically PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and determining under reducing conditions a level of  
20 dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, and wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is reversibly oxidized in a cell. In certain other embodiments of the present invention, a  
25 method is provided for identifying a TC45 protein tyrosine phosphatase (TC45) that is reversibly oxidized in a cell, comprising contacting a biological sample comprising a cell that comprises TC45 with a stimulus under conditions and for a time sufficient to induce reversible oxidation of TC45 in the cell; isolating anaerobically TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a  
30 sulfhydryl group of a TC45 active site invariant cysteine; and determining under reducing conditions a level of dephosphorylation of a detectably labeled TC45 substrate

by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM\_080422, and wherein detectable substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is reversibly oxidized in a cell.

5 In certain embodiments the protein tyrosine phosphatase is PTP1B, PTP-PEST, PTP $\gamma$ , LAR, MKP-1, CRYP $\alpha$ , PTP $\text{cryp2}$ , DEP-1, SAP1, PCPTP1, PTPSL, STEP, HePTP, PTPIA2, PTPNP, PTPNE6, PTP $\mu$ , PTPX1, PTPX10, SHP-1, SHP-2, PTPBEM1, PTPBEM2, PTPBYP, PTP $\text{esp}$ , PTP $\text{oc}$ , PTP-PEZ, PTP-MEG1, MEG2, LC-PTP, TC-PTP, TC45, CD45, LAR, cdc14, RPTP- $\alpha$ , RPTP- $\epsilon$ , RKPTP, LyPTP, PEP, BDP1, PTP20, PTPK1, PTPS31, PTPGMC, GLEPP1, OSTPTP, PTP $\text{tep}$ , PTPRL10, PTP2E, PTPD1, PTPD2, PTP36, PTPBAS, PTPBL, BTPBA14, PTP $\text{Typ}$ , HDPTP, PTPTD14, PTP $\alpha$ , PTP $\beta$ , PTP $\delta$ , PTP $\epsilon$ , PTP $\kappa$ , PTP $\lambda$ , PTP $\mu$ , PTP $\rho$ , PTP $\psi$ , PTP $\phi$ , PTP $\zeta$ , PTPNU3 or PTPH1, or a PTP as presented in Figure 8, or a dual specificity phosphatase including but not limited to PYST-1, MKP-1, MKP-2, MKP-4, MKP-5, MKP-7, hVH5, PAC1, VHR, or any dual specificity phosphatase disclosed in WO00/65069 (DSP-5), WO00/65068 (DSP-10), WO00/63393 (DSP-8), WO00/60100 (DSP-9), WO00/60099 (DSP-4), WO00/60098 (DSP-7), WO00/60092 (DSP-3), WO00/56899 (DSP-2), WO00/53636 (DSP-1), WO00/09656 (MKP), AU5475399 (MKP), AU8479498, WO99/02704, WO97/06245 (MKP), WO01/83723, WO01/57221, WO01/05983, WO01/02582, WO01/02581, U.S.A.N. 09/955,732 (DSP-15), U.S.A.N. 09/964,277 (DSP-16), U.S.A.N. 60/268,837 (DSP-17) or U.S.A.N. 60/291,476 (PTP). In certain embodiments the protein tyrosine phosphatase substrate comprises phosphorylated poly-(4:1)-Glu-Tyr, which in certain further embodiments comprises  $^{32}\text{P}$ . In certain embodiments the detectably labeled protein tyrosine phosphatase substrate comprises a reporter molecule that is a fluorophore, a radionuclide, a chemiluminescent agent, an enzyme, an immunologically detectable epitope or a chromophore. In certain further embodiments, the fluorophore is selected from fluorescein, rhodamine, Texas Red, AlexaFluor-594, AlexaFluor-488, Oregon Green, BODIPY-FL or Cy-5.

According to certain embodiments of the present invention, the protein tyrosine phosphatase substrate comprises a polypeptide sequence derived from a protein selected from a PDGF receptor, VCP, p130<sup>cas</sup>, EGF receptor, p210 bcr:abl, MAP

kinase, Shc, insulin receptor, lck, T cell receptor zeta chain, lysozyme, or reduced and carboxyamidomethylated and maleylated lysozyme (RCML). In certain embodiments the sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is an alkylating agent. In certain embodiments the sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is iodoacetamide, iodoacetic acid, arsenic oxide, maleimide analog, haloacetimido analog, 4-vinylpyrimidine analog or N-ethylmaleimide. In certain embodiments the cell is a mammalian cell, which in certain embodiments is derived from a cell line and in certain further embodiments is derived from Rat-1 fibroblasts, COS cells, CHO cells or HEK-293 cells. In certain embodiments the step of isolating the protein tyrosine phosphatase comprises cell lysis, and in certain further embodiments the step of isolating comprises gel electrophoresis of the protein tyrosine phosphatase, and in certain further embodiments this step comprises electrophoresis of the protein tyrosine phosphatase in a gel comprising the detectably labeled protein tyrosine phosphatase substrate. In certain embodiments the method further comprises detecting the protein tyrosine phosphatase with an antibody that specifically binds to the phosphatase.

In certain embodiments of the present invention the stimulus increases reactive oxygen species in the sample, and in certain further embodiments the stimulus is a cytokine, a growth factor, a hormone, a cell stressor or a peptide. In certain embodiments the cell stressor is ROS or ultraviolet light. In certain embodiments the stimulus is PDGF, EGF, bFGF, insulin, GM-CSF, TGF- $\beta$ 1, IL-1, IL-3, IFN- $\gamma$ , TNF- $\alpha$ , PHA, AT-2, thrombin, thyrotropin, parathyroid hormone, LPA, sphingosine-1-phosphate, serotonin, endothelin, acetylcholine, platelet activating factor, bradykinin or G-CSF.

In certain embodiments of the present invention there is provided a method for identifying a protein tyrosine phosphatase that is reversibly modified by a PTP active site-binding agent in a cell, comprising contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine with a biological sample comprising a cell



that comprises at least one protein tyrosine phosphatase; isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and determining, under conditions that are capable of reversing a reversible

5 modification of a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine, a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and therefrom identifying a protein tyrosine phosphatase that is reversibly modified by a

10 PTP active site-binding agent in a cell. In certain embodiments, the invention provides a method for identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is reversibly modified by a PTP active site-binding agent in a cell, comprising contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine with a biological sample comprising a

15 cell that comprises SHP-2; isolating SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group of a SHP-2 active site invariant cysteine, a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein

20 SHP-2 comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, and wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is reversibly modified by a PTP active site-binding agent in a cell. In another embodiment, the invention provides a method for identifying a PTP1B protein

25 tyrosine phosphatase (PTP1B) that is reversibly modified by a PTP active site-binding agent in a cell, comprising contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine with a biological sample comprising a cell that comprises PTP1B; isolating PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a

30 sulfhydryl group of a PTP1B active site invariant cysteine; and determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group

of a PTP1B active site invariant cysteine, a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, and wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is reversibly modified by a PTP active site-binding agent in a cell. In another embodiment, the invention provides a method for identifying a TC45 protein tyrosine phosphatase (TC45) that is reversibly modified by a PTP active site-binding agent in a cell, comprising contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine with a biological sample comprising a cell that comprises TC45; isolating TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine; and determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group of a TC45 active site invariant cysteine, a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM\_080422, and wherein detectable substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is reversibly modified by a PTP active site-binding agent in a cell.

In certain further embodiments, the step of isolating is performed anaerobically. In certain embodiments the PTP active site-binding agent is an agent that covalently binds to the PTP active site or an agent that non-covalently binds to the PTP active site. In certain embodiments the PTP active site-binding agent is a sulfonated compound or a vanadate compound. In certain embodiments the PTP active site-binding agent covalently and reversibly modifies a sulfhydryl group of a PTP active site invariant cysteine. In certain further embodiments the step of determining comprises reversing a covalent modification of a sulfhydryl group of a PTP active site invariant cysteine. In certain still further embodiments the step of reversing comprises contacting the PTP with a reducing agent. In certain still further embodiments the reducing agent is dithiothreitol, dithioerythritol or 2-mercaptoethanol. In certain embodiments the sulfhydryl-reactive agent that is capable of irreversibly modifying a

sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is iodoacetamide, iodoacetic acid, arsenic oxide, maleimide analog, haloacetimido analog, 4-vinylpyrimidine analog or N-ethylmaleimide.

According to certain other embodiments of the present invention, there is

5 provided a method for identifying a protein tyrosine phosphatase that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising contacting a biological sample comprising a cell that comprises at least one protein tyrosine phosphatase with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and

10 thereby reversibly protect protein tyrosine phosphatase active site invariant cysteine from modification; isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and determining, under conditions that reverse the reversible protection of the protein tyrosine phosphatase

15 active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and therefrom identifying a protein tyrosine phosphatase that is a reversibly modified component of an inducible biological

20 signaling pathway in a cell. In a certain embodiment, the invention provides a method for identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising contacting a biological sample comprising a cell that comprises SHP-2 with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to

25 induce the biological signaling pathway and thereby reversibly protect a SHP-2 active site invariant cysteine from modification; isolating the SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and determining, under conditions that reverse the reversible protection of the SHP-2 active site invariant cysteine from modification, a

30 level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2 comprises a polypeptide comprising an amino acid sequence set forth in any one

of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, and wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is a reversibly modified component of an inducible biological signaling pathway in a cell. In another embodiment, that which is provided is a method for

5 identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising contacting a biological sample comprising a cell that comprises PTP1B with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and thereby reversibly protect a PTP1B active

10 site invariant cysteine from modification; isolating the PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and determining, under conditions that reverse the reversible protection of the PTP1B active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B,

15 wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, and wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is a reversibly modified component of an inducible biological signaling pathway in a cell. In a certain embodiment, the invention provides a method for

20 identifying a TC45 protein tyrosine phosphatase (TC45) that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising contacting a biological sample comprising a cell that comprises TC45 with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and thereby reversibly protect a TC45 active site invariant

25 cysteine from modification; isolating the TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine; and determining, under conditions that reverse the reversible protection of the TC45 active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein TC45

30 comprises a polypeptide comprising an amino acid sequence set forth in NM\_080422, and wherein detectable substrate dephosphorylation indicates that an active TC45 is

present, and therefrom identifying a TC45 that is a reversibly modified component of an inducible biological signaling pathway in a cell.

In certain embodiments the step of isolating is performed anaerobically. In certain embodiments the sulfhydryl-reactive agent that is capable of irreversibly  
5 modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is iodoacetamide, iodoacetic acid, arsenic oxide, maleimide analog, haloacetimido analog, 4-vinylpyrimidine analog or N-ethylmaleimide.

In certain other embodiments the invention provides a method for identifying an agent that alters an inducible biological signaling pathway, comprising  
10 (a) identifying a protein tyrosine phosphatase that is reversibly oxidized in a first biological sample comprising a cell that comprises at least one PTP according to the above described method steps of contacting, isolating and determining; (b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises the PTP that is reversibly oxidized as identified  
15 according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of the PTP; (c) isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and (d) determining under reducing conditions a level of dephosphorylation of  
20 a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an  
25 inducible biological signaling pathway, and wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway. In certain  
30 embodiments the step of isolating in the method recited in (a) is performed

anaerobically, and in certain embodiments the step of isolating recited in (c) is performed anaerobically.

In a certain embodiment, the invention provides a method for identifying an agent that alters an inducible biological signaling pathway, comprising (a) identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is reversibly oxidized in a cell according to a method comprising (i) contacting a first biological sample comprising a cell that comprises SHP-2 with a stimulus under conditions and for a time sufficient to induce reversible oxidation of SHP-2 in the cell; (ii) isolating SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; (iii) determining under reducing conditions a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is reversibly oxidized in a cell; (b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises SHP-2 that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of SHP-2; (c) isolating SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and (d) determining under reducing conditions a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2 comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway, wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

In another embodiment of the invention is provided a method for identifying an agent that alters an inducible biological signaling pathway, comprising (a) identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is reversibly oxidized in a cell according to a method comprising (i) contacting a first biological sample comprising a cell that comprises PTP1B with a stimulus under conditions and for a time sufficient to induce reversible oxidation of PTP1B in the cell; (ii) isolating PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine; (iii) determining under reducing conditions a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is reversibly oxidized in a cell; (b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises PTP1B that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of PTP1B; (c) isolating PTP1B in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and (d) determining under reducing conditions a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway, and wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

The invention also provides a method for identifying an agent that alters an inducible biological signaling pathway, comprising (a) identifying a TC45 protein

tyrosine phosphatase (TC45) that is reversibly oxidized in a cell according to a method comprising (i) contacting a first biological sample comprising a cell that comprises TC45 with a stimulus under conditions and for a time sufficient to induce reversible oxidation of TC45 in the cell; (ii) isolating TC45 in the presence of a sulfhydryl-  
5 reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine; (iii) determining under reducing conditions a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein detectable substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is reversibly oxidized in a cell; (b) contacting, in the presence  
10 and absence of a candidate agent, a second biological sample comprising a cell that comprises TC45 that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of TC45; (c) isolating TC45 in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a TC45 active site invariant  
15 cysteine; and (d) determining under reducing conditions a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM\_080422, wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate  
20 dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway, and wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus  
25 in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

These and other aspects of the present invention will become evident upon reference to the following detailed description and attached drawings. In addition,  
30 various references are set forth herein which describe in more detail certain aspects of this invention, and are therefore incorporated by reference in their entireties.



## BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic for use of the “in-gel” phosphatase assay to identify PTPs that are susceptible to stimulus-induced oxidation.

5                Figure 2 shows reversible oxidation of multiple PTPs concomitant with tyrosine phosphorylation in Rat-1 cells treated with H<sub>2</sub>O<sub>2</sub>. Figure 2A illustrates an in-gel PTP assay. Serum-deprived Rat-1 cells were exposed to various concentrations of H<sub>2</sub>O<sub>2</sub> for 1 min, harvested, and lysed in the absence (lane 1) or presence (lanes 2-7) of 10 mM iodoacetic acid (IAA). Figure 2B presents an immunoblot of tyrosine  
10 phosphorylated proteins immunoprecipitated from lysates of H<sub>2</sub>O<sub>2</sub>-treated cells with Ab PT-66, then immunoblotted with anti-pTyr Ab (G104). Figure 2C presents an in-gel PTP assay. After pre-incubation of Rat-1 cells in the absence or presence of 30 mM NAC, the cells were exposed to 200 μM H<sub>2</sub>O<sub>2</sub> and lysed in the presence of 10 mM IAA at the indicated times. Figure 2D shows an in-gel PTP assay of oxidized PTPs. Rat-1  
15 cells were serum-starved in the absence or presence of 2.5 mM BSO for 16 h. H<sub>2</sub>O<sub>2</sub> (200 μM) was added for 2 minutes, then removed by washing the cells with fresh culture media. Incubation was continued until the cells were harvested in lysis buffer containing 10 mM IAA at the times indicated. Arrows indicate PTPs for which reduction/reactivation displayed dependence on intracellular GSH.

20                Figure 3 illustrates that H<sub>2</sub>O<sub>2</sub>-induced mitogenic signaling was associated with inactivation of PTPs. Figure 3A presents an in-gel PTP assay. Purified SHP-2 (E76A mutant, 1 ng/lane) was incubated with PBS, H<sub>2</sub>O<sub>2</sub>, or t-BHP at 37 °C for 5 minutes. Aliquots were then incubated at room temperature for an additional 5 minutes, either in the absence (- IAA) or presence (+IAA) of 4 mM IAA. Figure 3B  
25 shows images of ROS-induced DCF fluorescence in Rat-1 cells pre-loaded with 20 μM H<sub>2</sub>DCFDA in the dark and then exposed to H<sub>2</sub>O<sub>2</sub> or t-BHP (each at 200 μM). The cells are shown at magnification 400X (upper panels). Cells (1 x 10<sup>5</sup>) that underwent the same treatment as above were harvested and resuspended in Hanks' solution, then immediately subjected to flow cytometric analysis to measure ROS-induced DCF  
30 fluorescence (lower panels). The basal peak indicates background fluorescence, whereas the rightward shifted peak indicates ROS-induced DCF fluorescence. Figure

3C depicts an in-gel PTP assay of oxidized PTPs. Cells were exposed to H<sub>2</sub>O<sub>2</sub> and t-BHP (each at 200  $\mu$ M) for the indicated times and lysed in the presence of 10 mM IAA. Figure 3D presents an immunoblot of cell lysates prepared from cells exposed to H<sub>2</sub>O<sub>2</sub> and t-BHP (each at 200  $\mu$ M). Tyrosine phosphorylated proteins were immunoprecipitated with Ab PT-66, followed by immunoblotting with anti-pTyr Ab G104 (upper panel). An aliquot of lysate from each treatment was immunoblotted with anti-phospho-MAPK Ab and subsequently with anti-MAPK Ab (lower panel).

Figure 4 shows PDGF induced oxidation of a 70k PTP in Rat-1 cells. Figure 4A represents an in-gel PTP assay. Serum-starved Rat-1 cells were exposed to 50 ng/ml PDGF-BB for the times indicated. Lysates were prepared in the presence of 10 mM IAA and subjected to in-gel PTP assay. The arrow indicates a 70 kDa PTP that was transiently oxidized following stimulation of Rat-1 cells with PDGF. The result shown is representative of four independent experiments. Figure 4B: Cells were pre-incubated in the absence or presence of 30 mM NAC for 40 minutes. Excess NAC was removed prior to addition of PDGF (50 ng/ml). PDGF-induced oxidation of the 70 kDa PTP, which was impaired in the presence of NAC (arrow), was visualized by the modified in-gel PTP assay. Figure 4C: Cells were treated with NAC and PDGF as described above. PDGFR was immunoprecipitated from lysates with Ab-X and immunoblotted with anti-pTyr Ab G104. The same filter was subsequently re-probed with Ab-X (upper panels). Aliquots of cell lysate from each treatment were immunoblotted with anti-phospho-MAPK Ab and re-probed with anti-MAPK Ab (lower panels).

Figure 5 illustrates identification of the 70kDa PTP that was susceptible to PDGF-induced oxidation as SHP-2. Figure 5A: Serum-starved Rat-1 cells were exposed to PDGF (50 ng/ml) for the indicated times. The PDGFR and associated proteins were immunoprecipitated with antibody Ab-X, and pTyr proteins were visualized by immunoblotting with anti-pTyr Ab G104 (upper panel). The same filter was re-probed with anti-PDGFR, anti-SHP-2, anti-GAP, and anti-p85 PI3K Abs. The positions of PDGFR (solid arrow) and SHP-2 (open arrow) are indicated. Figure 5B: Rat-1 cells, either untreated (-) or stimulated with 50 ng/ml PDGF (+), were harvested in lysis buffer containing 10 mM IAA. Lysates were incubated with antibody specific

for either SHP-2 or SHP-1 and subjected to an in-gel PTP assay (upper panel). The arrow denotes the position of the 70 kDa PTP that was inactivated in response to PDGF and immunodepleted from cell lysates with antibodies to SHP-2. The lower panel illustrates an immunoblot to show the immunodepletion of SHP-2.

5                   Figure 6 demonstrates oxidation and inactivation of SHP-2 that was induced by PDGF but not by EGF or FGF. Figure 6A: Rat-1 cells were incubated with 20  $\mu$ M CM-H<sub>2</sub>DCFDA in the dark for 20 minutes, then exposed to peptide growth factors (50 ng/ml) for an additional 10 mins. Images of ROS-induced DCF fluorescence are shown at 50X magnification. The data are representative of four  
10 independent experiments. Figure 6B presents an in-gel PTP assay of oxidized PTPs. Cells were exposed to peptide growth factors for the indicated times and lysed in the presence of 10 mM IAA. Figure 6C illustrates an immunoblot of cell lysates from each treatment group immunoblotted with anti-phospho-MAPK Ab (upper panel). The immunoblot was reprobed with anti-MAPK Ab (lower panel).

15                   Figure 7 shows that the pool of PDGFR-associated SHP-2, which was oxidized and inactivated in response to PDGF, was also involved in down-regulation of MAPK signaling. Rat-1 cells were transiently transfected with plasmids expressing WT or Y1009F mutant G-CSFR/PDGFR chimeric receptor, or with a plasmid encoding Green Fluorescence Protein (GFP) as a control for expression. Figure 7A: After  
20 exposure to 100 ng/ml G-CSF for 5 min, the chimeric receptors were immunoprecipitated from lysates with antibody Ab-X and immunoblotted with anti-pTyr Ab G104. Immunoprecipitation of the receptors was verified by immunoblotting with Ab-X. The same filter was stripped and reprobed with anti-SHP-2 Ab. Expression of the chimeric receptors was verified by immunoblotting an aliquot of each lysate with  
25 Ab-X, which recognizes the intracellular segment of the PDGFR, and subsequently with anti-G-CSFR Ab, which recognizes the extracellular segment of chimeric receptors. Figure 7B presents an in-gel PTP assay of Rat-1 cell lysates. Transfected Rat-1 cells were treated with G-CSF for the indicated times and then lysed in the presence of 10 mM IAA. The arrow denotes the position of SHP-2. Figure 7C: The  
30 wild-type and mutant chimeric receptors were immunoprecipitated at the indicated times and immunoblotted with anti-pTyr Ab (G104) (top panel). The same filter was

re-probed with anti-PDGFR Ab-X (bottom panel). Figure 7D presents an immunoblot of cell lysates from each treatment blotted with anti-phospho-MAPK Ab (upper panel), and then re-probed with anti-MAPK Ab (lower panel). Figure 7E presents a densitometric analysis of the gel image, which illustrates the ratio of phosphorylated  
5 MAPK (upper panel of 7D) over total MAPK (lower panel of 7D).

Figure 8 presents a listing of PTPs.

Figure 9 illustrates an in-gel PTP assay that shows protection from IAA-inactivation of PTP activity in PHA-stimulated peripheral blood mononuclear lymphocytes pre-treated with a PTP active site-binding agent.

10 Figure 10 illustrates that hydrogen peroxide is a mediator of insulin signaling. Figure 10A presents images of ROS-induced DCF fluorescence by fluorescence microscopy (50x magnification) of serum-starved Rat-1 cells exposed to 50 nM insulin. The data are representative of three independent experiments. Figure 10B: Rat-1 cells were transiently transfected with different quantities of plasmid  
15 encoding human catalase. Two days after transfection, cells were serum-deprived and then stimulated with 50 nM insulin (INS) for 10 min. The cells were lysed, and catalase expression was verified by immunoblotting with anti-catalase antibody (top panel). The insulin receptor  $\beta$  (IR- $\beta$ ) subunit was immunoprecipitated from 400  $\mu$ g of lysate with antibody 29B4. Immunoblotting was performed with anti-pYpY<sup>1162/1163</sup>, and  
20 subsequently with anti-IR- $\beta$  antibody clone C-19 as a loading control (middle panel). An aliquot of lysate (30  $\mu$ g) was subjected to immunoblotting with anti-phospho-PKB/AKT antibody. The same filter was then stripped and re-probed with anti-PKB/AKT antibody as a loading control (bottom panel).

Figure 11 shows that insulin induced the transient oxidation of PTP1B  
25 and TC45. For each experiment, serum-starved Rat-1 cells were exposed to 50 nM insulin for the indicated times. Lysates were prepared under anaerobic conditions in the presence of 10 mM IAA and then subjected to in-gel PTP assays. Figure 11A: The arrowheads indicate that 50 kDa and 45 kDa PTPs were transiently oxidized in response to insulin. Figure B and Figure C present in-gel PTP assays. Total lysate (400  $\mu$ g) was  
30 immunoprecipitated with normal IgG (labeled C), anti-PTP1B antibody (FG6), or anti-TC45 antibody (1910H) coupled to protein G-Sepharose beads. After

immunoprecipitation, the immune complexes and supernatants were subjected to in-gel PTP assays. Figure 11B shows immunodepletion of the 50 kDa PTP from the lysate with anti-PTP1B antibody. Figure 11C illustrates immunodepletion of the 45 kDa PTP with antibody specific for TC45. The lane marked "Lys" represents cell lysate prior to immunodepletion. The lower panels illustrate immunoblots of total lysate and the supernatants following immunodepletion, using either anti-PTP1B antibody (Figure 11B, lower panels) or anti-TC45 antibody (Figure 11C, lower panels). The same blots were subsequently reprobed with anti-SHP-2 antibody to ensure loading of equal amounts of protein.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a method of identifying any PTP that has been reversibly modified (*e.g.*, oxidized, or reversibly modified by a PTP active site-binding agent) in a cellular context (*i.e.*, within a cell, or *in vivo*), and in particular to any modification of a PTP active site invariant cysteine residue that can be reversed with a reducing agent. As described herein, typically such modification/ oxidation of a PTP is accompanied by transient inactivation of the enzyme. Described herein is the unexpected discovery that reversible oxidation of a PTP in a cellular context renders such a PTP resistant to irreversible inactivation of the enzyme by a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a PTP active site invariant cysteine. This discovery is exploited to provide the invention method in a manner whereby one or more PTPs of interest may be non-specifically isolated from a cell—the invention method thus does not require any specific preparation and/or purification of a particular PTP that may be suspected of undergoing reversible modification/ oxidation *in vivo*, such as recombinant cloning and expression of the PTP (which would require a polynucleotide encoding each PTP of interest) or immunoprecipitation of the PTP (which would require an antibody specific for each PTP of interest). Instead, the method may be practiced using a cell that comprises one or a plurality of PTPs, where the method permits determination of one or more reversibly modified/ oxidized PTPs in a cell even where the identities of the particular PTPs that are expressed in the cell are not known *a priori*.

Accordingly, the one or more PTPs in a cell that are transiently modified/ oxidized at the time the cell is contacted with the sulfhydryl-reactive agent that is capable of irreversibly (*e.g.*, covalently) modifying a sulfhydryl group of a PTP active site invariant cysteine are not inactivated by the sulfhydryl-reactive agent, and such PTPs can subsequently be detected on the basis of their ability to catalytically dephosphorylate a PTP substrate after reversal (*e.g.*, under reducing conditions) of the transient modification/ oxidation event. Hence, and according to non-limiting theory, contact with a stimulus may induce a biological signaling pathway in a cell, which pathway comprises at least one PTP (and potentially a plurality of PTPs) that is reversibly modified at invariant cysteine (*e.g.*, oxidized to form sulfenic acid) in response to the stimulus, and which is therefore reversibly protected from irreversible modification of its active site invariant cysteine during subsequent isolation of the PTP in the presence of a sulfhydryl-reactive agent (*e.g.*, iodoacetamide) that is capable of so modifying the invariant cysteine. By way of contrast, any PTPs that are not reversibly and protectively modified in the course of the cellular response to the stimulus will be susceptible to permanent inactivation by the sulfhydryl agent during the PTP isolation procedure. Isolated PTPs are then exposed to conditions that reverse the reversible protection from modification of the PTP active site invariant cysteine (*e.g.*, reducing conditions), such that PTP enzyme activity is restored only to those PTPs that have undergone the reversible protective modification. This activity can then be determined as a level of dephosphorylation of a detectably labeled PTP substrate as described herein. While this non-limiting theoretical model of the PTP modifications that may or may not occur in the course of practicing the subject invention method pertains to reversible oxidation of PTP active site invariant cysteine in response to a stimulus, as described herein the invention is not intended to be so limited, and also contemplates any other reversible modification to a PTP (*e.g.*, by transient occupancy of the PTP active site by a PTP active site-binding agent that is capable of reversibly modifying a PTP active site invariant cysteine) that can be reversed, for example, a modification that is reversed by a reducing agent.

In certain embodiments the invention thus also provides a method for identifying a PTP that is a reversibly oxidized component of an inducible biological

signaling pathway that is induced by a stimulus which may trigger reversible modification, for example, oxidation, of one or more PTPs. In such embodiments, any stimulus that is known to be, or suspected of being, capable of inducing a biological signaling pathway is contacted with a cell comprising one or a plurality of PTPs, and  
5 recoverable PTP catalytic activity is assessed following inactivation of unmodified (*e.g.*, non-oxidized) PTPs with a sulfhydryl-reactive agent that is capable of irreversibly (*e.g.*, covalently) modifying a sulfhydryl group of a PTP active site invariant cysteine. In certain related embodiments, prior to the step of contacting the cell with a stimulus, the cell may be contacted with a PTP active site-binding agent, to determine whether  
10 such a PTP active site-binding agent alters (*i.e.*, increases or decreases in a statistically significant manner) the level of substrate dephosphorylation by one or more PTPs present in the cell, where PTPs that have retained the ability to dephosphorylate substrate have been reversibly and protectively modified (*e.g.*, oxidized) as a result of the biological signaling pathway induced by the stimulus. Non-limiting examples of  
15 PTP active site-binding agents for use in such embodiments include PTP inhibitors as disclosed in Zhang et al. (2002 *Ann. Rev. Pharmacol. Toxicol.* 42:209-234), Iverson et al. (2001 *Biochemistry* 40:14812-20) and Jia et al. (2001 *J. Med. Chem.* 44:4584). Certain such agents may be sulfonated compounds or vanadate compounds (*e.g.*, sodium orthovanadate); these and other PTP active site-binding agents are known to the  
20 art and/or may be identified according to established methodologies, including those described herein and in the cited references.

As described in greater detail below, in certain preferred embodiments determination of PTP substrate dephosphorylation, by one or more reversibly oxidized PTPs isolated anaerobically from a cell in the presence of a sulfhydryl-reactive agent  
25 that is capable of covalently modifying a sulfhydryl group of a PTP active site invariant cysteine on any unmodified PTP, is accomplished using a modified "in-gel" PTP activity assay to allow visualization of a profile of PTPs that are reversibly oxidized following a particular stimulus. Anaerobic isolation conditions may be employed for one or more PTPs identified according to the present method, and whether and/or to  
30 what extent such conditions may be needed will vary with each PTP, as well as with the nature of the reversible modification (*i.e.*, oxidative *vs.* non-oxidative) experienced by

the PTP in a cell. Typically, anaerobic isolation of one or more PTPs relates to performing procedures for isolation of PTPs from a sample in an environment that is substantially reduced in its exposure to or content of oxygen gas, for instance, by conducting the isolation in an enclosure in which ambient air has been substantially replaced by an inert gas such as argon or nitrogen. Other procedures for creating an anaerobic atmosphere for PTP isolation may also be employed and will be familiar to those skilled in the art in view of the present disclosure, which describes examples of oxidative modification of PTPs that are detected following anaerobic isolation of the PTP.

Exemplary results using the modified "in-gel" PTP activity assay provided herein indicated that several PTPs could be identified that were oxidized and inactivated reversibly in Rat-1 cells following stimulation with H<sub>2</sub>O<sub>2</sub>, and that this event was important for peroxide-induced mitogenic signaling. Examples provided below show that platelet-derived growth factor (PDGF) stimulation of Rat-1 cells induced the oxidation and inhibition of the SH2 domain-containing PTP known as SHP-2 (*see Hof et al., 1998 Cell 92:441-50*), which facilitated mitogenic signaling in these cells in response to the growth factor. Additional examples provided show that insulin-induced signaling resulted in the oxidation and inhibition of two PTPs, PTP1B and the 45 kDa spliced variant of TC-PTP, TC45 (*see Mosinger et al., 1992 Proc. Natl. Acad. Sci. USA 89:499-503; Tiganis et al., 1998 Mol. Cell Biol. 18:1622-34; Tiganis et al., 1999 J. Biol. Chem. 274:27768-75*). The invention contemplates extending these analyses to identify and characterize other PTPs and their roles in the control of a broad array of biological signal transduction pathways.

Certain preferred embodiments of the invention therefore relate to a method wherein stimulus-induced oxidation within a cellular context (*i.e., in vivo*) provides a means of "tagging" (*e.g., reversibly protecting from a sulfhydryl-reactive agent*) those PTPs that are integral to the regulation of the cellular signal transduction pathways initiated by that stimulus. Alkylation with a sulfhydryl-reactive agent that is capable of covalently, and preferably irreversibly, modifying a sulfhydryl group of a PTP active site invariant cysteine, for example, iodoacetamide (IAA), can be used to inactivate and thereby functionally subtract out the bulk of the PTPs, which being



unaffected by the stimulus and hence not transiently oxidized, are unprotected from the  
sulfhydryl reagent. Following reduction to reverse the transient oxidation and return  
the transiently inactivated PTP to an active state, the stimulus-responsive (*i.e.*,  
oxidatively protected) PTPs can be isolated and identified on the basis of phosphatase  
5 activity, demonstrable as dephosphorylation of a PTP substrate using any of a variety of  
well established procedures as provided herein and as known to the art. (See, *e.g.*, Flint  
et al., 1993 *EMBO J.* 12:1937-1946; Tonks et al., 1991 *Meths. Enzymol.* 201:427-42;  
Tonks et al., 1988 *J. Biol. Chem.* 263:6722). Reducing conditions that are suitable for  
determining PTP substrate dephosphorylation by a catalytically competent phosphatase  
10 (*i.e.*, an "active" PTP) can be achieved using compositions and methods well known to  
the art in view of the present disclosure. The precise reducing conditions may vary as a  
function of the particular PTP for which activity following reversible inactivation is to  
be determined; common reducing agents for establishing such conditions include, by  
way of illustration and not limitation, dithiothreitol (Cleland's reagent), dithioerythritol  
15 and 2-mercaptoethanol ( $\beta$ -mercaptoethanol).

The "in-gel" phosphatase assay described herein comprises a  
modification of an existing technique (Burridge and Nelson, 1995 *Anal. Biochem.* 232,  
56-64) and provides one such preferred procedure for demonstrating PTP activity  
toward (phosphorylated) PTP substrates as provided herein. The modified in-gel  
20 phosphatase assay features electrophoretic separation and renaturation, under reducing  
conditions, of a plurality of PTPs in a gel impregnated with a detectably labeled PTP  
substrate, but with regard to the step of determining dephosphorylation of a detectably  
labeled PTP substrate by a PTP according to the methods of disclosed herein, the  
invention is not intended to be so limited. For example some PTPs, in particular certain  
25 of the receptor-like forms, may not renature efficiently in the "in-gel" PTP activity  
assay (Burridge and Nelson, 1995). The invention therefore contemplates incorporation  
of any suitable method for determining a level of dephosphorylation of a detectably  
labeled PTP substrate by a PTP, which may vary according to the physicochemical  
properties (*e.g.*, conformational stability in a variety of chemical environments) of  
30 particular PTPs, and which can be selected by a person having ordinary skill in the art  
readily and without undue experimentation based on the instant disclosure.

For example, suitable phosphatase assays may include in-gel assays using non-denaturing gel systems. Additional methodologies for assaying PTP-mediated substrate dephosphorylation may include proteomics-based strategies, for example, using solid-phase immobilized, broad specificity PTP active site-directed inhibitors (such as phenylarsine oxide coupled to agarose) as affinity matrices for the purification and identification of oxidation-sensitive PTPs. As also noted above, other embodiments contemplate exposure of cells comprising an inducible biological signaling pathway to one or more PTP active site-binding agents (*e.g.*, Zhang et al. 2002 *Ann. Rev. Pharmacol. Toxicol.* 42:209-234; Iverson et al. 2001 *Biochemistry* 40:14812-20; Jia et al. 2001 *J. Med. Chem.* 44:4584) prior to contacting these cells with a stimulus that induces the signaling pathway. Recoverable activity may then be assayed in PTPs that are protectively modified, by reversible oxidation, when the PTPs are isolated in the presence of a sulfhydryl-reactive agent, wherein further the active site-binding agent may be employed to facilitate PTP isolation. By combining these approaches with the use of substrate-trapping mutant forms of the PTPs thus identified (*e.g.*, Flint et al., 1997 *Proc. Natl. Acad. Sci. USA* 94:1680-1685), the physiological substrate specificities of these enzymes can be determined to further characterize the components of biological signaling pathways that comprise PTPs. Additional characterization of biological signaling pathway components identified using the methods of the present invention may be achieved using specific binding proteins to detect such components. Preferred examples of such binding proteins include antibodies, receptors, counterreceptors, ligands, and the like, for example, an antibody that, as provided herein, specifically binds to a phosphatase, or an antibody that specifically binds to a phosphopeptide such as phosphotyrosine, phosphoserine or phosphothreonine.

## PTPs

As used herein, a phosphatase is a member of the PTP family if it contains the signature motif [I/V]HCXAGXXR[S/T]G (SEQ ID NO:98). Dual specificity PTPs, *i.e.*, PTPs which dephosphorylate both phosphorylated tyrosine and phosphorylated serine or threonine, are also suitable for use in the invention.

Appropriate PTPs for use in the present invention include any PTP family member, for example, any PTP described in Andersen et al. (2001 *Mol. Cell. Biol.* 21:7117) or shown in Figure 8, or any dual specificity phosphatase including but not limited to PYST-1, MKP-1, MKP-2, MKP-4, MKP-5, MKP-7, hVH5, PAC1, VHR, or any dual

5 specificity phosphatase disclosed in WO00/65069 (DSP-5), WO00/65068 (DSP-10), WO00/63393 (DSP-8), WO00/60100 (DSP-9), WO00/60099 (DSP-4), WO00/60098 (DSP-7), WO00/60092 (DSP-3), WO00/56899 (DSP-2), WO00/53636 (DSP-1), WO00/09656 (MKP), AU5475399 (MKP), AU8479498, WO99/02704, WO97/06245 (MKP), WO01/83723, WO01/57221, WO01/05983, WO01/02582, WO01/02581,

10 U.S.A.N. 09/955,732 (DSP-15), U.S.A.N. 09/964,277 (DSP-16), U.S.A.N. 60/268,837 (DSP-17) or U.S.A.N. 60/291,476 (PTP) and in certain preferred embodiments including, but not limited to, PTP1B (*e.g.*, GenBank Accession Nos. M31724 (SEQ ID NOS: 1-2); NM\_002827 (SEQ ID NOS: 3-4); NM\_011201 (SEQ ID NOS: 5-6); M31724 (SEQ ID NOS: 7-8); M33689 (SEQ ID NOS: 9-10); M33962 (SEQ ID NOS:

15 11-12)), PTP-PEST (*e.g.*, GenBank Accession Nos. D13380 (SEQ ID NOS: 68-69); M93425 (SEQ ID NOS: 70-71); S69184 (SEQ ID NOS: 72-73); X86781 (SEQ ID NOS: 74-75); D38072 (SEQ ID NOS: 76-77)), PTP $\gamma$ , LAR, MKP-1, CRYPA, PTPcrp2, DEP-1 (*e.g.*, GenBank Accession Nos. U10886 (SEQ ID NOS: 41-42); D37781 (SEQ ID NOS: 43-44); AAB26475 (SEQ ID NO: 45); D45212 (SEQ ID NOS:

20 46-47); U40790 (SEQ ID NOS: 48-49)), SAP1, PCPTP1, PTPSL, STEP, HePTP, PTPIA2, PTPNP, PTPNE6, PTP $\mu$ , PTPX1, PTPX10, SHP-1 (*e.g.*, GenBank Accession Nos. M74903 (SEQ ID NOS: 86-87); X62055 (SEQ ID NOS: 88-89); M77273 (SEQ ID NOS: 90-91); X82817 (SEQ ID NO: 92); X82818 (SEQ ID NO: 93); M90388 (SEQ ID NOS: 94-95); U77038 (SEQ ID NOS: 96-97)), SHP-2 (*e.g.*, GenBank Accession

25 Nos. D13540 (SEQ ID NOS: 25-26); L03535 (SEQ ID NOS: 27-28); L07527 (SEQ ID NOS: 29-30); X70766 (SEQ ID NOS: 31-32); L08807 (SEQ ID NO: 33); S78088 (SEQ ID NOS: 34-35); S39383 (SEQ ID NO: 36); D84372 (SEQ ID NOS: 13-14); U09307 (SEQ ID NOS: 15-16)), PTPBEM1, PTPBEM2, PTPBYP, PTPesp, PTPoc, PTP-PEZ, PTP-MEG1, MEG2, LC-PTP, TC-PTP (*e.g.*, GenBank Accession Nos. M25393 (SEQ

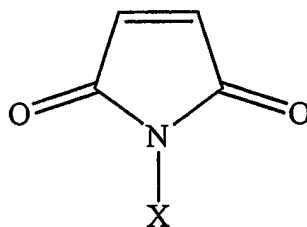
30 ID NOS: 17-18); M81478 (SEQ ID NO: 19); M80737 (SEQ ID NO: 20); M81477 (SEQ ID NOS: 21-22); X58828 (SEQ ID NOS: 23-24); NM\_002828 (SEQ ID NOS:

\_\_\_\_ and \_\_\_\_), TC45 (*e.g.*, NM\_080422 (SEQ ID NOS: \_\_\_\_ and \_\_\_\_)), CD45 (*e.g.*,  
 GenBank Accession Nos. Y00638 (SEQ ID NOS: 78-79); Y00062 (SEQ ID NOS: 80-  
 81); M92933 (SEQ ID NOS: 82-83); M10072 (SEQ ID NOS: 84-85); LAR, cdc14  
 (which includes cdc14a (*e.g.*, GenBank Accession Nos. AF122013 (SEQ ID NOS: 50-  
 51); AF064102 (SEQ ID NOS: 52-53); AF064103 (SEQ ID NOS: 54-55); Li et al.,  
 1997 *J. Biol. Chem.* 272:29403; U.S. Patent No. 6,331,614) and cdc14b (*e.g.*, GenBank  
 Accession Nos. AF064104 (SEQ ID NOS: 56-57); AF064105 (SEQ ID NOS: 58-59);  
 AF023158 (SEQ ID NOS: 60-61); Li et al., 1997 *J. Biol. Chem.* 272:29403), RPTP- $\alpha$ ,  
 RPTP- $\epsilon$ , RKPTP, LyPTP, PEP, BDP1, PTP20, PTPK1, PTPS31, PTPGMC, GLEPP1,  
 10 OSTPTP, PTPtep, PTPRL10, PTP2E, PTPD1, PTPD2, PTP36, PTPBAS, PTPBL,  
 BTPBA14, PTPTyp, HDPTP, PTPTD14, PTP $\alpha$ , PTP $\beta$ , PTP $\delta$ , PTP $\epsilon$  (*e.g.*, GenBank  
 Accession Nos. X54134 (SEQ ID NOS: 62-63); D83484 (SEQ ID NOS: 64-65);  
 D78610 (SEQ ID NOS: 66-67)), PTP $\kappa$ , PTP $\lambda$ , PTP $\mu$ , PTP $\rho$ , PTP $\psi$ , PTP $\phi$ , PTP $\zeta$ ,  
 PTPNU3 and PTPH1 (*e.g.*, GenBank Accession Nos. M64572 (SEQ ID NOS: 37-38)  
 15 and S39392 (SEQ ID NOS: 39-40)), and mutated forms thereof.

As noted above, and particularly with regard to the identification and  
 selection of suitable PTP substrates as provided herein, including peptide fragments  
 having sequences derived from portions of polypeptides identified as physiological PTP  
 substrates, the present invention relates in part to the use of substrate trapping mutant  
 20 protein tyrosine phosphatases (PTPs) derived from a PTP that has been mutated in a  
 manner that does not cause significant alteration of the Michaelis-Menten constant  
 ( $K_m$ ) of the enzyme, but which results in a reduction of the catalytic rate constant  
 ( $K_{cat}$ ). In certain embodiments, the PTP catalytic domain invariant aspartate residue  
 may be replaced with another amino acid. In certain other embodiments, the substrate  
 25 trapping mutant PTP may be mutated by replacement of a catalytic domain cysteine  
 residue. Under certain conditions *in vivo*, a PTP enzyme may itself undergo tyrosine  
 phosphorylation in a manner that can alter interactions between the PTP and other  
 molecules, including PTP substrates. Thus, in certain embodiments the substrate  
 trapping mutant PTP may be further mutated by replacement of at least one tyrosine  
 30 residue with an amino acid that is not capable of being phosphorylated. Substrate  
 trapping mutant PTPs are disclosed, for example, in U.S. Patent Nos. 5,912,138 and

5,951,979 and in U.S. Application No. 09/334,575. Disclosure relating to the preparation and use of substrate trapping mutant PTPs, including PTPs having at least one tyrosine residue replaced with an amino acid that is not capable of being phosphorylated, and including identification of physiological PTP substrates, can be found in WO 00/75339.

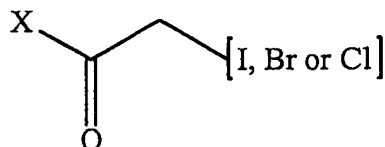
According to particularly preferred embodiments of the methods of the present invention, PTPs in which the wildtype catalytic domain invariant cysteine residues are present, may be inactivated by sulfhydryl-reactive agents according to assay methods as disclosed herein. Preferably, such agents are sulfhydryl-reactive agents that are capable of covalently and irreversibly modifying a sulfhydryl group of a PTP active site invariant cysteine, for example alkylating agents such as N-ethylmaleimide (NEM), iodoacetamide (IAA) or iodoacetic acid. Other sulfhydryl-reactive agents that are capable of covalently modifying a sulfhydryl group of a PTP active site invariant cysteine include arsenic oxide; 4-vinyl pyridine and analogs and derivatives thereof; maleimide analogs conforming to the following structural formula:



wherein X is the remainder of the molecule, including linkers;

20

or halo-acetamido analogs conforming to the following structural formula:



25

wherein X is the remainder of the molecule, including linkers.

Useful sulfhydryl-reactive agents may also include other cysteine-reactive compounds, *i.e.*, chemically reactive species that covalently modify cysteine and/or adjacent residues, further including such compounds which do so stoichiometrically and without selectivity for PTP proteins or polypeptides.

The term "isolated" means that the material is removed from its original environment (*e.g.*, the natural environment if it is naturally occurring). For example, a naturally occurring nucleic acid or polypeptide present in a living animal is not isolated, but the same nucleic acid or polypeptide, separated from some or all of the co-existing materials in the natural system, is isolated. Such nucleic acid could be part of a vector and/or such nucleic acid or polypeptide could be part of a composition (*e.g.*, a cell lysate), and still be isolated in that such vector or composition is not part of the natural environment for the nucleic acid or polypeptide. The term "gene" means the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding region "leader and trailer" as well as intervening sequences (introns) between individual coding segments (exons).

#### SAMPLES

According to the present invention, there is provided a method of identifying a protein tyrosine phosphatase that has been reversibly oxidized, typically in a biological sample. A "sample" as used herein refers to a biological sample containing at least one protein tyrosine phosphatase, and may be provided by obtaining a blood sample, biopsy specimen, tissue explant, organ culture or any other tissue or cell preparation from a subject or a biological source. A sample may further refer to a tissue or cell preparation in which the morphological integrity or physical state has been disrupted, for example, by dissection, dissociation, solubilization, fractionation, homogenization, biochemical or chemical extraction, pulverization, lyophilization, sonication or any other means for processing a sample derived from a subject or biological source. In certain preferred embodiments, the sample is a cell that comprises at least one PTP, and in certain particularly preferred embodiments the cell comprises an inducible biological signaling pathway, at least one component of which is a PTP.

In particularly preferred embodiments the cell is a mammalian cell, for example, Rat-1 fibroblasts, COS cells, CHO cells, HEK-293 cells or other well known model cell lines, which are available from the American Type Culture Collection (ATCC, Manassas, VA).

5                   The subject or biological source may be a human or non-human animal, a primary cell culture or culture adapted cell line including but not limited to genetically engineered cell lines that may contain chromosomally integrated or episomal recombinant nucleic acid sequences, immortalized or immortalizable cell lines, somatic cell hybrid cell lines, differentiated or differentiatable cell lines, transformed cell lines  
10 and the like. Optionally, in certain situations it may be desirable to treat cells in a biological sample with hydrogen peroxide and/or with another agent that directly or indirectly promotes reactive oxygen species (ROS) generation, including biological stimuli as described herein; in certain other situations it may be desirable to treat cells in a biological sample with a ROS scavenger, such as N-acetyl cysteine (NAC) or  
15 superoxide dismutase (SOD) or other ROS scavengers known in the art; in other situations cellular glutathione (GSH) may be depleted by treating cells with L-buthionine-SR-sulfoximine (Bso); and in other circumstances cells may be treated with pervanadate to enrich the sample in tyrosine phosphorylated proteins. Other means may also be employed to effect an increase in the population of tyrosine phosphorylated  
20 proteins present in the sample, including the use of a subject or biological source that is a cell line that has been transfected with at least one gene encoding a protein tyrosine kinase.

                  Additionally or alternatively, a biological signaling pathway may be induced in subject or biological source cells by contacting such cells with an  
25 appropriate stimulus, which may vary depending upon the signaling pathway under investigation, whether known or unknown. For example, a signaling pathway that, when induced, results in protein tyrosine phosphorylation and/or protein tyrosine dephosphorylation may be stimulated in subject or biological source cells using any one or more of a variety of well known methods and compositions known in the art to  
30 stimulate protein tyrosine kinase and/or PTP activity. These stimuli may include, without limitation, exposure of cells to cytokines, growth factors, hormones, peptides,

small molecule mediators, cell stressors (e.g., ultraviolet light; temperature shifts; osmotic shock; ROS or a source thereof, such as hydrogen peroxide, superoxide, ozone, etc. or any agent that induces or promotes ROS production (see, e.g., Halliwell and Gutteridge, *Free Radicals in Biology and Medicine* (3<sup>rd</sup> Ed.) 1999 Oxford University Press, Oxford, UK); heavy metals; alcohol) or other agents that induce PTK-mediated protein tyrosine phosphorylation and/or PTP-mediated phosphoprotein tyrosine dephosphorylation. Such agents may include, for example, interleukins (e.g., IL-1, IL-3), interferons (e.g., IFN- $\gamma$ ), human growth hormone, insulin, epidermal growth factor (EGF), platelet derived growth factor (PDGF), granulocyte colony stimulating factor (G-CSF), granulocyte-megakaryocyte colony stimulating factor (GM-CSF), transforming growth factor (e.g., TGF- $\beta$ 1), tumor necrosis factor (e.g., TNF- $\alpha$ ) and fibroblast growth factor (FGF; e.g., basic FGF (bFGF)), any agent or combination of agents capable of triggering T lymphocyte activation via the T cell receptor for antigen (TCR; TCR-inducing agents may include superantigens, specifically recognized antigens and/or MHC-derived peptides, MHC peptide tetramers (e.g., Altman et al., 1996 *Science* 274:94-96) TCR-specific antibodies or fragments or derivatives thereof, lectins (e.g., PHA, PWM, ConA, etc.), mitogens, G-protein coupled receptor agonists such as angiotensin-2, thrombin, thyrotropin, parathyroid hormone, lysophosphatidic acid (LPA), sphingosine-1-phosphate, serotonin, endothelin, acetylcholine, platelet activating factor (PAF) or bradykinin, as well as other agents with which those having ordinary skill in the art will be familiar (see, e.g., Rhee et al., 10 October 2000 *Science's stke*, <[http://www.stke.org/cgi/content/full/OC\\_sigtrans;2000/53/pel](http://www.stke.org/cgi/content/full/OC_sigtrans;2000/53/pel), and references cited therein; see also Gross et al., 1999 *J. Biol. Chem.* 274:26378-86; Prenzel et al., 1999 *Nature* 402:884-88; Ushio-Fukai et al., 1999 *J. Biol. Chem.* 274:22699-704; Holland et al., 1998 *Endothelium* 6:113-21; Daub et al., 1997 *EMBO J.* 16:7032-44; Kyprianou et al., 1997 *Prostate* 32:266-71; Marumo et al., 1997 *Circulation* 96:2361-67).

As noted above, regulated tyrosine phosphorylation contributes to specific pathways for biological signal transduction, including those associated with cell division, cell survival, apoptosis, proliferation and differentiation, and "inducible signaling pathways" in the context of the present invention include transient or stable



associations or interactions among molecular components involved in the control of these and similar processes in cells. Depending on the particular pathway of interest, an appropriate parameter for determining induction of such pathway may be selected. For example, for signaling pathways associated with cell proliferation, there is available a variety of well known methodologies for quantifying proliferation, including, for example, incorporation of tritiated thymidine into cellular DNA, monitoring of detectable (*e.g.*, fluorimetric or colorimetric) indicators of cellular respiratory activity, or cell counting, or the like. Similarly, in the cell biology arts there are known multiple techniques for assessing cell survival (*e.g.*, vital dyes, metabolic indicators, etc.) and for determining apoptosis (*e.g.*, annexin V binding, DNA fragmentation assays, caspase activation, etc.). Other signaling pathways will be associated with particular cellular phenotypes, for example specific induction of gene expression (*e.g.*, detectable as transcription or translation products, or by bioassays of such products, or as nuclear localization of cytoplasmic factors), altered (*e.g.*, statistically significant increases or decreases) levels of intracellular mediators (*e.g.*, activated kinases or phosphatases, altered levels of cyclic nucleotides or of physiologically active ionic species, etc.), or altered cellular morphology, and the like, such that cellular responsiveness to a particular stimulus as provided herein can be readily identified to determine whether a particular cell comprises an inducible signaling pathway.

For example, a biological signaling pathway may be induced in a cell by a stimulus that induces or promotes ROS production. Cells may be stimulated with any one or more of a number of stimuli as provided herein, including those provided above, such as a cytokine, a growth factor (*e.g.*, PDGF), a hormone such as a polypeptide hormone (*e.g.*, insulin), a cell stressor, or a peptide. Intracellular production of ROS, including hydrogen peroxide, may be determined according to established methodologies using direct or indirect ROS indicators, for example, by using fluorescent ROS indicators such as 2',7'-dichlorofluorescein diacetate (H<sub>2</sub>DCFDA) or 5-(and-6)-chloromethyl-2',7'-dichlorodihydrofluorescein diacetate (CM-H<sub>2</sub>DCFDA). ROS-induced DCF fluorescence can then be measured, for instance, by fluorimetry, fluorescence microscopy or flow cytofluorimetry, or according to other methods known in the art. ROS may also be detected in biological systems by any of a variety of other

techniques, including spin trapping, in which a reactive radical is allowed to react with a molecular trap to produce a long-lived radical, and also including molecular fingerprinting, which measures end-products of oxidative damage. Specific compositions and methods for such trapping, as well as other means for determining  
5 ROS, are known to the art and selection of a technique for identifying ROS may depend upon the particular reactive oxygen species that is to be detected (*see, e.g.,* Halliwell and Gutteridge, *supra*).

The effect of ROS production on phosphorylation and/or dephosphorylation of one or more polypeptide components of a signaling pathway may  
10 be examined by determining the level of phosphorylation of components in the particular pathway. For example, treatment of Rat-1 cells with PDGF, which has been shown to induce ROS production in various cell types (Bae et al., 2000, *supra*; Sundaresan et al. *supra*), results in a rapid increase in the tyrosine phosphorylation of cellular proteins and enhanced phosphorylation of MAPKs (*see also* Bazenet et al.,  
15 1996 *Mol. Cell Biol.* 16:6926-36; Klinghoffer et al., 2001 *Mol. Cell* 78:343-54; Yu et al., 2000 *J. Biol. Chem.* 275:19076-82). As another example, the effect of ROS production in the signal transduction pathway induced by insulin may be evaluated by determining the level of tyrosine phosphorylation of insulin receptor beta (IR- $\beta$ ) and/or of the downstream signaling molecule PKB/Akt and/or of any other downstream  
20 polypeptide that may be a component of a particular signal transduction pathway as provided herein.

A number of methods are described herein and known in the art for detection of one or more particular signal transduction pathway component polypeptides, and for determination of whether such polypeptides may be tyrosine-  
25 phosphorylated in cells following stimulation as described herein. Also described herein are methods for detecting such polypeptides, including determination of altered (*i.e.,* increased or decreased with statistical significance) tyrosine phosphorylation that may further include determination of the phosphorylation state of particular tyrosine residues at specified positions within a polypeptide sequence, which altered tyrosine  
30 phosphorylation may in certain embodiments be accompanied by the presence or absence of ROS production in the cells from which such polypeptides are obtained

(*e.g.*, as a result of exposure to a stimulus). Non-limiting examples of such detection methods include the use of reagents that specifically bind to signaling pathway components, for example, by immunological methods (*e.g.*, immunoprecipitation, immunoblotting, ELISA, radioimmunoprecipitation, and the like) that employ  
5 antibodies as provided herein that are capable of specifically binding a particular signaling pathway component polypeptide or a particular tyrosine-phosphorylated polypeptide. Additionally and as described in greater detail herein, in certain embodiments cellular ROS production induced by a stimulus may be partially or completely impaired, abrogated, inhibited or otherwise counteracted by inclusion of a  
10 ROS-neutralizing agent, for instance, by the presence of enzymes such as catalase ( $\text{H}_2\text{O}_2\text{:H}_2\text{O}_2$  oxidoreductase) or superoxide dismutase (SOD; superoxide:superoxide oxidoreductase), or of free-radical scavengers or other agents known to the art that are capable of neutralizing the effects of ROS (*see, e.g.*, Halliwell and Gutteridge, *supra*).

15

#### SUBSTRATES

In preferred embodiments, a PTP substrate may be any naturally or non-naturally occurring phosphorylated peptide, polypeptide or protein that can specifically bind to and/or be dephosphorylated by a PTP (including dual specificity phosphatases)  
20 as provided herein, or any other phosphorylated molecule that can be a substrate of a PTP family member as provided herein. Non-limiting examples of known PTP substrates include the proteins VCP (*see, e.g.*, Zhang et al., 1999 *J. Biol. Chem.* 274:17806, and references cited therein), p130<sup>cas</sup>, EGF receptor, p210 bcr:abl, MAP kinase, Shc (Tiganis et al., 1998 *Mol. Cell. Biol.* 18:1622-1634), insulin receptor, lck  
25 (lymphocyte specific protein tyrosine kinase, Marth et al., 1985 *Cell* 43:393), T cell receptor zeta chain, and phosphatidylinositol 3,4,5-triphosphate (Maehama et al., 1998 *J. Biol. Chem.* 273:13375).

As another example, tyrosine phosphorylated peptides identified with mutant PTPs from peptide libraries by the methods of Songyang et al. (1995 *Nature*  
30 373:536-539; 1993 *Cell* 72:767-778) can be used herein in place of the complete tyrosine phosphorylated protein in PTP binding and/or catalytic assays. Optionally,

candidate peptide sequences may be selected and optimized for dephosphorylation or binding activity as described herein using other techniques such as affinity selection followed by mass spectrometric detection (*e.g.*, Pellegrini et al., 1998 *Biochemistry* 37:15598; Huyer et al., 1998 *Anal. Biochem.* 258:19) or by "inverse alanine scanning" (*e.g.*, Vetter et al., 2000 *J. Biol. Chem.* 275:2265). In certain particularly preferred embodiments, a PTP substrate is a tyrosine phosphorylated peptide, which may include a partial amino acid sequence, portion, region, fragment, variant, derivative or the like from a naturally or non-naturally tyrosine-phosphorylated peptide, polypeptide or protein that can specifically bind to and/or be dephosphorylated by a PTP. In preferred  
10 embodiments, the PTP substrate is detectably labeled as provided herein, such that it can be detectably dephosphorylated by a PTP family member, as also provided herein. A PTP substrate that is a tyrosine phosphorylated peptide typically comprises 2-700 amino acids. Preferred substrates as described herein include a random amino acid copolymer of poly-Glu-Tyr wherein the Glu:Tyr ratio is approximately 4:1; preparations of this copolymer may be polydisperse with respect to molecular mass and  
15 in certain preferred embodiments may have an average molecular mass of approximately 55-65 kDa. Other preferred substrates include reduced and carboxyamidomethylated and maleylated lysozyme (RCML, Flint et al., 1993 *EMBO J.* 12:1937-1946). In certain other embodiments, a PTP substrate may comprise a  
20 phosphotyrosine residue having an attached fluorescent label.

Identification and selection of PTP substrates as provided herein, for use in the present invention, may be performed according to procedures with which those having ordinary skill in the art will be familiar, or may, for example, be conducted according to the disclosures of WO 00/75339 or U.S. Application Number 09/334,575  
25 and references cited therein. The phosphorylated protein/PTP complex may be isolated, for example, by conventional isolation techniques as described in U.S. Patent No. 5,352,660, including salting out, chromatography, electrophoresis, gel filtration, fractionation, absorption, polyacrylamide gel electrophoresis, agglutination, combinations thereof or other strategies. PTP substrates that are known may also be  
30 prepared according to well known procedures that employ principles of molecular biology and/or peptide synthesis (*e.g.*, Ausubel et al., 1993 *Current Protocols in*

*Molecular Biology*, Greene Publ. Assoc. Inc. & John Wiley & Sons, Inc., Boston, MA; Sambrook et al., 1989 *Molecular Cloning*, Second Ed., Cold Spring Harbor Laboratory, Plainview, NY; Fox, 1995 *Molec. Biotechnol.* 3:249; Maeji et al., 1995 *Pept. Res.* 8:33).

The PTP substrate peptides of the present invention may therefore be  
5 derived from PTP substrate proteins, polypeptides and peptides as provided herein  
having amino acid sequences that are identical or similar to tyrosine phosphorylated  
PTP substrate sequences known in the art. For example by way of illustration and not  
limitation, peptide sequences derived from the known PTP substrate proteins referred to  
above are contemplated for use according to the instant invention, as are peptides  
10 having at least 70% similarity (preferably 70% identity), more preferably 90%  
similarity (more preferably 90% identity) and still more preferably 95% similarity (still  
more preferably 95% identity) to the polypeptides described in references cited herein  
and in the Examples and to portions of such polypeptides as disclosed herein. As  
known in the art "similarity" between two polypeptides is determined by comparing the  
15 amino acid sequence and conserved amino acid substitutes thereto of the polypeptide to  
the sequence of a second polypeptide (e.g., using GENWORKS, Align or the BLAST  
algorithm, or another algorithm, as described above).

Thus, according to the present invention, substrates may include full  
length tyrosine phosphorylated proteins and polypeptides as well as fragments (e.g.,  
20 portions), derivatives or analogs thereof that can be phosphorylated at a tyrosine  
residue. Such fragments, derivatives and analogs include any PTP substrate  
polypeptide that retains at least the biological function of interacting with a PTP as  
provided herein, for example by forming a complex with a PTP and/or, in certain  
embodiments, undergoing PTP-catalyzed dephosphorylation. A fragment, derivative or  
25 analog of a peptide, protein or polypeptide as provided herein, including a PTP  
substrate polypeptide, and further including PTP substrates that are fusion proteins, may  
be (i) one in which one or more of the amino acid residues are substituted with a  
conserved or non-conserved amino acid residue (preferably a conserved amino acid  
residue), and such substituted amino acid residue may or may not be one encoded by  
30 the genetic code, or (ii) one in which one or more of the amino acid residues includes a  
substituent group, or (iii) one in which the substrate polypeptide is fused with another

compound, such as a compound to increase the half-life of the polypeptide (e.g., polyethylene glycol) or a detectable moiety such as a reporter molecule, or (iv) one in which additional amino acids are fused to the substrate polypeptide, including amino acids that are employed for purification of the substrate polypeptide or a proprotein  
5 sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art.

Certain preferred substrates include phosphoproteins and phosphopeptide sequences that may be tyrosine phosphorylated and/or serine/threonine phosphorylated, for example, as may provide suitable phosphophorylated substrates for  
10 dual specificity phosphatases, which are described above. Examples of physiological substrates which may provide phosphoprotein or phosphopeptides sequences for use as PTP substrates, including fragments, variants and derivatives as provided herein, include PDGF receptor, VCP, p130<sup>cas</sup>, EGF receptor, p210 bcr:abl, MAP kinase, Shc, insulin receptor, lck, and T cell receptor zeta chain. A number of non-physiological  
15 phosphoproteins and phosphopeptides are also known to be suitable PTP substrates, as described, for example, by Tonks et al. (1991 *Meths. Enzymol.* 201:427-42; 1988 *J. Biol. Chem.* 263:6722); these include, as non-limiting examples, poly-[Glu-Tyr], MBP and reduced and carboxyamidomethylated and maleylated lysozyme (RCML, Flint et al., 1993 *EMBO J.* 12:1937-1946).

20 In preferred embodiments the PTP substrate is detectably labeled, and in particularly preferred embodiments the PTP substrate is capable of generating a radioactive or a fluorescent signal. The PTP substrate can be detectably labeled by covalently or non-covalently attaching a suitable reporter molecule or moiety, for example a radionuclide such as <sup>32</sup>P (e.g., Pestka et al., 1999 *Protein Expr. Purif.*  
25 17:203-14), a radiohalogen such as iodine [<sup>125</sup>I or <sup>131</sup>I] (e.g., Wilbur, 1992 *Bioconjug. Chem.* 3:433-70), or tritium [<sup>3</sup>H]; an enzyme; or any of various luminescent (e.g., chemiluminescent) or fluorescent materials (e.g., a fluorophore) selected according to the particular fluorescence detection technique to be employed, as known in the art and based upon the present disclosure. Fluorescent reporter moieties and methods for  
30 labeling PTP substrates as provided herein can be found, for example in Haugland (1996 *Handbook of Fluorescent Probes and Research Chemicals- Sixth Ed.*, Molecular

Probes, Eugene, OR; 1999 *Handbook of Fluorescent Probes and Research Chemicals- Seventh Ed.*, Molecular Probes, Eugene, OR, <http://www.probes.com/lit/>) and in references cited therein. Particularly preferred for use as such a fluorophore in the subject invention methods are fluorescein, rhodamine, Texas Red, AlexaFluor-594, 5 AlexaFluor-488, Oregon Green, BODIPY-FL, umbelliferone, dichlorotriazinylamine fluorescein, dansyl chloride, phycoerythrin or Cy-5. Examples of suitable enzymes include, but are not limited to, horseradish peroxidase, biotin, alkaline phosphatase,  $\beta$ -galactosidase and acetylcholinesterase. Appropriate luminescent materials include luminol, and suitable radioactive materials include radioactive phosphorus [ $^{32}\text{P}$ ].

10

#### ANTIBODIES

Also contemplated by the present invention is the use according to certain embodiments of an antibody that specifically binds to a PTP, which may include peptides, polypeptides, and other non-peptide molecules that specifically bind to a PTP. 15 As used herein, a molecule is said to "specifically bind" to a PTP if it reacts at a detectable level with the PTP, but does not react detectably with peptides containing an unrelated sequence, or a sequence of a different phosphatase. Preferred binding molecules include antibodies, which may be, for example, polyclonal, monoclonal, single chain, chimeric, anti-idiotypic, or CDR-grafted immunoglobulins, or fragments 20 thereof, such as proteolytically generated or recombinantly produced immunoglobulin F(ab')<sub>2</sub>, Fab, Fv, and Fd fragments. Binding properties of an antibody to a PTP may generally be assessed using immunodetection methods including, for example, an enzyme-linked immunosorbent assay (ELISA), immunoprecipitation, immunoblotting and the like, which may be readily performed by those having ordinary skill in the art. 25 In certain preferred embodiments, the invention method may comprise isolating one or more particular PTPs with an antibody that specifically binds to each phosphatase; such embodiments may include without limitation methodologies for immuno-isolation (*e.g.*, immunoprecipitation, immunoaffinity chromatography) and/or immunodetection (*e.g.*, western blot) of at least one PTP.

30

Methods well known in the art may be used to generate antibodies, polyclonal antisera or monoclonal antibodies that are specific for a PTP; a number of

PTP-specific antibodies are also commercially available. Antibodies also may be produced as genetically engineered immunoglobulins (Ig) or Ig fragments designed to have desirable properties. For example, by way of illustration and not limitation, antibodies may include a recombinant IgG that is a chimeric fusion protein having at least one variable (V) region domain from a first mammalian species and at least one constant region domain from a second, distinct mammalian species. Most commonly, a chimeric antibody has murine variable region sequences and human constant region sequences. Such a murine/human chimeric immunoglobulin may be "humanized" by grafting the complementarity determining regions (CDRs) derived from a murine antibody, which confer binding specificity for an antigen, into human-derived V region framework regions and human-derived constant regions. Fragments of these molecules may be generated by proteolytic digestion, or optionally, by proteolytic digestion followed by mild reduction of disulfide bonds and alkylation. Alternatively, such fragments may also be generated by recombinant genetic engineering techniques.

As used herein, an antibody is said to be "immunospecific" or to "specifically bind" a PTP polypeptide if it reacts at a detectable level with PTP, preferably with an affinity constant,  $K_a$ , of greater than or equal to about  $10^4 \text{ M}^{-1}$ , more preferably of greater than or equal to about  $10^5 \text{ M}^{-1}$ , more preferably of greater than or equal to about  $10^6 \text{ M}^{-1}$ , and still more preferably of greater than or equal to about  $10^7 \text{ M}^{-1}$ . Affinities of binding partners or antibodies can be readily determined using conventional techniques, for example, those described by Scatchard et al. (*Ann. N.Y. Acad. Sci. USA* 51:660 (1949)) and by surface plasmon resonance (SPR; BIAcore™, Biosensor, Piscataway, NJ). For surface plasmon resonance, target molecules are immobilized on a solid phase and exposed to ligands in a mobile phase running along a flow cell. If ligand binding to the immobilized target occurs, the local refractive index changes, leading to a change in SPR angle, which can be monitored in real time by detecting changes in the intensity of the reflected light. The rates of change of the surface plasmon resonance signal can be analyzed to yield apparent rate constants for the association and dissociation phases of the binding reaction. The ratio of these values gives the apparent equilibrium constant (affinity). See, e.g., Wolff et al., *Cancer Res.* 53:2560-2565 (1993).



Antibodies may generally be prepared by any of a variety of techniques known to those having ordinary skill in the art. *See, e.g., Harlow et al., Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory (1988). In one such technique, an animal is immunized with PTP as an antigen to generate polyclonal antisera. Suitable  
5 animals include, for example, rabbits, sheep, goats, pigs, cattle, and may also include smaller mammalian species, such as mice, rats, and hamsters, or other species.

An immunogen may be comprised of cells expressing PTP, purified or partially purified PTP polypeptides or variants or fragments (*e.g., peptides*) thereof, or PTP peptides. PTP peptides may be generated by proteolytic cleavage or may be  
10 chemically synthesized. For instance, nucleic acid sequences encoding PTP polypeptides are provided herein, such that those skilled in the art may routinely prepare these polypeptides for use as immunogens. Polypeptides or peptides useful for immunization may also be selected by analyzing the primary, secondary, and tertiary structure of PTP according to methods known to those skilled in the art, in order to  
15 determine amino acid sequences more likely to generate an antigenic response in a host animal. *See, e.g., Novotny, 1991 Mol. Immunol. 28:201-207; Berzofsky, 1985 Science 229:932-40.*

Preparation of the immunogen for injection into animals may include covalent coupling of the PTP polypeptide (or variant or fragment thereof), to another  
20 immunogenic protein, for example, a carrier protein such as keyhole limpet hemocyanin (KLH) or bovine serum albumin (BSA). In addition, the PTP peptide, polypeptide, or PTP-expressing cells to be used as immunogen may be emulsified in an adjuvant. *See, e.g., Harlow et al., Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory (1988). In general, after the first injection, animals receive one or more booster  
25 immunizations according to a preferred schedule that may vary according to, *inter alia*, the antigen, the adjuvant (if any) and/or the particular animal species. The immune response may be monitored by periodically bleeding the animal, separating the sera out of the collected blood, and analyzing the sera in an immunoassay, such as an ELISA or Ouchterlony diffusion assay, or the like, to determine the specific antibody titer. Once  
30 an antibody titer is established, the animals may be bled periodically to accumulate the polyclonal antisera. Polyclonal antibodies that bind specifically to the PTP polypeptide

or peptide may then be purified from such antisera, for example, by affinity chromatography using protein A, or the PTP polypeptide, immobilized on a suitable solid support.

Monoclonal antibodies that specifically bind to PTP polypeptides or  
5 fragments or variants thereof, and hybridomas, which are immortal eukaryotic cell lines, that produce monoclonal antibodies having the desired binding specificity, may also be prepared, for example, using the technique of Kohler and Milstein (*Nature*, 256:495-497; 1976, *Eur. J. Immunol.* 6:511-519 (1975)) and improvements thereto. An animal—for example, a rat, hamster, or preferably mouse—is immunized with a PTP  
10 immunogen prepared as described above. Lymphoid cells that include antibody-forming cells, typically spleen cells, are obtained from an immunized animal and may be immortalized by fusion with a drug-sensitized myeloma (*e.g.*, plasmacytoma) cell fusion partner, preferably one that is syngeneic with the immunized animal and that optionally has other desirable properties (*e.g.*, inability to express endogenous Ig gene  
15 products). The lymphoid (*e.g.*, spleen) cells and the myeloma cells may be combined for a few minutes with a membrane fusion-promoting agent, such as polyethylene glycol or a nonionic detergent, and then plated at low density on a selective medium that supports the growth of hybridoma cells, but not unfused myeloma cells. A preferred selection media is HAT (hypoxanthine, aminopterin, thymidine). After a  
20 sufficient time, usually about one to two weeks, colonies of cells are observed. Single colonies are isolated, and antibodies produced by the cells may be tested for binding activity to the PTP polypeptide, or variant or fragment thereof. Hybridomas producing monoclonal antibodies with high affinity and specificity for a PTP antigen are preferred. Hybridomas that produce monoclonal antibodies that specifically bind to a PTP  
25 polypeptide or variant or fragment thereof are therefore contemplated by the present invention.

Monoclonal antibodies may be isolated from the supernatants of hybridoma cultures. An alternative method for production of a murine monoclonal antibody is to inject the hybridoma cells into the peritoneal cavity of a syngeneic  
30 mouse, for example, a mouse that has been treated (*e.g.*, pristane-primed) to promote formation of ascites fluid containing the monoclonal antibody. Contaminants may be

removed from the subsequently (usually within 1-3 weeks) harvested ascites fluid by conventional techniques, such as chromatography, gel filtration, precipitation, extraction, or the like. For example, antibodies may be purified by affinity chromatography using an appropriate ligand selected based on particular properties of the monoclonal antibody (e.g., heavy or light chain isotype, binding specificity, etc.).  
5 Examples of a suitable ligand, immobilized on a solid support, include Protein A, Protein G, an anti-constant region (light chain or heavy chain) antibody, an anti-idiotypic antibody and a PTP polypeptide or fragment or variant thereof.

Human monoclonal antibodies may be generated by any number of techniques with which those having ordinary skill in the art will be familiar. Such methods include but are not limited to, Epstein Barr Virus (EBV) transformation of human peripheral blood cells (e.g., containing B lymphocytes), *in vitro* immunization of human B cells, fusion of spleen cells from immunized transgenic mice carrying human immunoglobulin genes inserted by yeast artificial chromosomes (YAC), isolation from  
15 human immunoglobulin V region phage libraries, or other procedures as known in the art and based on the disclosure herein.

For example, one method for generating human monoclonal antibodies includes immortalizing human peripheral blood cells by EBV transformation. *See, e.g.,* U.S. Patent No. 4,464,456. An immortalized cell line producing a monoclonal antibody that specifically binds to a PTP polypeptide (or a variant or fragment thereof) can be  
20 identified by immunodetection methods as provided herein, for example, an ELISA, and then isolated by standard cloning techniques. Another method to generate human monoclonal antibodies, *in vitro* immunization, includes priming human splenic B cells with antigen, followed by fusion of primed B cells with a heterohybrid fusion partner.  
25 *See, e.g.,* Boerner et al., 1991 *J. Immunol.* 147:86-95.

Still another method for the generation of human PTP-specific monoclonal antibodies and polyclonal antisera for use in the present invention relates to transgenic mice. *See, e.g.,* U.S. Patent No. 5,877,397; Bruggemann et al., 1997 *Curr. Opin. Biotechnol.* 8:455-58; Jakobovits et al., 1995 *Ann. N. Y. Acad. Sci.* 764:525-35.  
30 In these mice, human immunoglobulin heavy and light chain genes have been artificially introduced by genetic engineering in germline configuration, and the

endogenous murine immunoglobulin genes have been inactivated. *See, e.g.,* Bruggemann et al., 1997 *Curr. Opin. Biotechnol.* 8:455-58. For example, human immunoglobulin transgenes may be mini-gene constructs, or transloci on yeast artificial chromosomes, which undergo B cell-specific DNA rearrangement and hypermutation in the mouse lymphoid tissue. *See, Bruggemann et al., 1997 Curr. Opin. Biotechnol.* 8:455-58. Human monoclonal antibodies specifically binding to PTP may be obtained by immunizing the transgenic animals, fusing spleen cells with myeloma cells, selecting and then cloning cells producing antibody, as described above. Polyclonal sera containing human antibodies may also be obtained from the blood of the immunized animals.

Chimeric antibodies, specific for a PTP, including humanized antibodies, may also be generated according to the present invention. A chimeric antibody has at least one constant region domain derived from a first mammalian species and at least one variable region domain derived from a second, distinct mammalian species. *See, e.g.,* Morrison et al., 1984, *Proc. Natl. Acad. Sci. USA*, 81:6851-55. In preferred embodiments, a chimeric antibody may be constructed by cloning the polynucleotide sequence that encodes at least one variable region domain derived from a non-human monoclonal antibody, such as the variable region derived from a murine, rat, or hamster monoclonal antibody, into a vector containing a nucleic acid sequence that encodes at least one human constant region. *See, e.g.,* Shin et al., 1989 *Methods Enzymol.* 178:459-76; Walls et al., 1993 *Nucleic Acids Res.* 21:2921-29. By way of example, the polynucleotide sequence encoding the light chain variable region of a murine monoclonal antibody may be inserted into a vector containing a nucleic acid sequence encoding the human kappa light chain constant region sequence. In a separate vector, the polynucleotide sequence encoding the heavy chain variable region of the monoclonal antibody may be cloned in frame with sequences encoding the human IgG1 constant region. The particular human constant region selected may depend upon the effector functions desired for the particular antibody (*e.g.,* complement fixing, binding to a particular Fc receptor, etc.). Another method known in the art for generating chimeric antibodies is homologous recombination (*e.g.,* U.S. Patent No. 5,482,856).

Preferably, the vectors will be transfected into eukaryotic cells for stable expression of the chimeric antibody.

A non-human/human chimeric antibody may be further genetically engineered to create a "humanized" antibody. Such a humanized antibody may  
5 comprise a plurality of CDRs derived from an immunoglobulin of a non-human mammalian species, at least one human variable framework region, and at least one human immunoglobulin constant region. Humanization may in certain embodiments provide an antibody that has decreased binding affinity for a PTP when compared, for example, with either a non-human monoclonal antibody from which a PTP binding  
10 variable region is obtained, or a chimeric antibody having such a V region and at least one human C region, as described above. Useful strategies for designing humanized antibodies may therefore include, for example by way of illustration and not limitation, identification of human variable framework regions that are most homologous to the non-human framework regions of the chimeric antibody. Without wishing to be bound  
15 by theory, such a strategy may increase the likelihood that the humanized antibody will retain specific binding affinity for a PTP, which in some preferred embodiments may be substantially the same affinity for a PTP polypeptide or variant or fragment thereof, and in certain other preferred embodiments may be a greater affinity for PTP. *See, e.g., Jones et al., 1986 Nature 321:522-25; Riechmann et al., 1988 Nature 332:323-27.*  
20 Designing such a humanized antibody may therefore include determining CDR loop conformations and structural determinants of the non-human variable regions, for example, by computer modeling, and then comparing the CDR loops and determinants to known human CDR loop structures and determinants. *See, e.g., Padlan et al., 1995 FASEB 9:133-39; Chothia et al., 1989 Nature, 342:377-383.* Computer modeling may  
25 also be used to compare human structural templates selected by sequence homology with the non-human variable regions. *See, e.g., Bajorath et al., 1995 Ther. Immunol. 2:95-103; EP-0578515-A3.* If humanization of the non-human CDRs results in a decrease in binding affinity, computer modeling may aid in identifying specific amino acid residues that could be changed by site-directed or other mutagenesis techniques to  
30 partially, completely or supra-optimally (*i.e.*, increase to a level greater than that of the non-humanized antibody) restore affinity. Those having ordinary skill in the art are

familiar with these techniques, and will readily appreciate numerous variations and modifications to such design strategies.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments or F(ab')<sub>2</sub> fragments, which may be prepared by proteolytic digestion with papain or pepsin, respectively. The antigen binding fragments may be separated from the Fc fragments by affinity chromatography, for example, using immobilized protein A or protein G, or immobilized PTP polypeptide, or a suitable variant or fragment thereof. Those having ordinary skill in the art can routinely and without undue experimentation determine what is a suitable variant or fragment based on characterization of affinity purified antibodies obtained, for example, using immunodetection methods as provided herein. An alternative method to generate Fab fragments includes mild reduction of F(ab')<sub>2</sub> fragments followed by alkylation. See, e.g., Weir, *Handbook of Experimental Immunology*, 1986, Blackwell Scientific, Boston.

According to certain embodiments, non-human, human, or humanized heavy chain and light chain variable regions of any of the above described Ig molecules may be constructed as single chain Fv (sFv) polypeptide fragments (single chain antibodies). See, e.g., Bird et al., 1988 *Science* 242:423-426; Huston et al., 1988 *Proc. Natl. Acad. Sci. USA* 85:5879-5883. Multi-functional sFv fusion proteins may be generated by linking a polynucleotide sequence encoding an sFv polypeptide in-frame with at least one polynucleotide sequence encoding any of a variety of known effector proteins. These methods are known in the art, and are disclosed, for example, in EP-B1-0318554, U.S. Patent No. 5,132,405, U.S. Patent No. 5,091,513, and U.S. Patent No. 5,476,786. By way of example, effector proteins may include immunoglobulin constant region sequences. See, e.g., Hollenbaugh et al., 1995 *J. Immunol. Methods* 188:1-7. Other examples of effector proteins are enzymes. As a non-limiting example, such an enzyme may provide a biological activity for therapeutic purposes (see, e.g., Siemers et al., 1997 *Bioconjug. Chem.* 8:510-19), or may provide a detectable activity, such as horseradish peroxidase-catalyzed conversion of any of a number of well-known substrates into a detectable product, for diagnostic uses. Still other examples of sFv fusion proteins include Ig-toxin fusions, or immunotoxins, wherein the sFv polypeptide

is linked to a toxin. Those having ordinary skill in the art will appreciate that a wide variety of polypeptide sequences have been identified that, under appropriate conditions, are toxic to cells. As used herein, a toxin polypeptide for inclusion in an immunoglobulin-toxin fusion protein may be any polypeptide capable of being  
5 introduced to a cell in a manner that compromises cell survival, for example, by directly interfering with a vital function or by inducing apoptosis. Toxins thus may include, for example, ribosome-inactivating proteins, such as *Pseudomonas aeruginosa* exotoxin A, plant gelonin, bryodin from *Bryonia dioica*, or the like. See, e.g., Thrush et al., 1996 *Annu. Rev. Immunol.* 14:49-71; Frankel et al., 1996 *Cancer Res.* 56:926-32. Numerous  
10 other toxins, including chemotherapeutic agents, anti-mitotic agents, antibiotics, inducers of apoptosis (or "apoptogens", see, e.g., Green and Reed, 1998, *Science* 281:1309-1312), or the like, are known to those familiar with the art, and the examples provided herein are intended to be illustrative without limiting the scope and spirit of the invention.

15 The sFv may, in certain embodiments, be fused to peptide or polypeptide domains that permit detection of specific binding between the fusion protein and antigen (e.g., a PTP). For example, the fusion polypeptide domain may be an affinity tag polypeptide. Binding of the sFv fusion protein to a binding partner (e.g., a PTP) may therefore be detected using an affinity polypeptide or peptide tag, such as an  
20 avidin, streptavidin or a His (e.g., polyhistidine) tag, by any of a variety of techniques with which those skilled in the art will be familiar. Detection techniques may also include, for example, binding of an avidin or streptavidin fusion protein to biotin or to a biotin mimetic sequence (see, e.g., Luo et al., 1998 *J. Biotechnol.* 65:225 and references cited therein), direct covalent modification of a fusion protein with a detectable moiety  
25 (e.g., a labeling moiety), non-covalent binding of the fusion protein to a specific labeled reporter molecule, enzymatic modification of a detectable substrate by a fusion protein that includes a portion having enzyme activity, or immobilization (covalent or non-covalent) of the fusion protein on a solid-phase support.

The sFv fusion protein of the present invention, comprising a PTP-specific immunoglobulin-derived polypeptide fused to another polypeptide such as an  
30 effector peptide having desirable affinity properties, may therefore include, for

example, a fusion protein wherein the effector peptide is an enzyme such as glutathione-S-transferase. As another example, sFv fusion proteins may also comprise a PTP-specific Ig polypeptide fused to a *Staphylococcus aureus* protein A polypeptide; protein A encoding nucleic acids and their use in constructing fusion proteins having  
5 affinity for immunoglobulin constant regions are disclosed generally, for example, in U.S. Patent 5,100,788. Other useful affinity polypeptides for construction of sFv fusion proteins may include streptavidin fusion proteins, as disclosed, for example, in WO 89/03422; U.S. 5,489,528; U.S. 5,672,691; WO 93/24631; U.S. 5,168,049; U.S. 5,272,254 and elsewhere, and avidin fusion proteins (see, *e.g.*, EP 511,747). As  
10 provided herein, sFv polypeptide sequences may be fused to fusion polypeptide sequences, including effector protein sequences, that may include full length fusion polypeptides and that may alternatively contain variants or fragments thereof.

An additional method for selecting antibodies that specifically bind to a PTP polypeptide or variant or fragment thereof is by phage display. *See, e.g.*, Winter et al., 1994 *Annul. Rev. Immunol.* 12:433-55; Burton et al., 1994 *Adv. Immunol.*  
15 57:191-280. Human or murine immunoglobulin variable region gene combinatorial libraries may be created in phage vectors that can be screened to select Ig fragments (Fab, Fv, sFv, or multimers thereof) that bind specifically to a PTP polypeptide or variant or fragment thereof. *See, e.g.*, U.S. Patent No. 5,223,409; Huse et al., 1989  
20 *Science* 246:1275-81; Kang et al., 1991 *Proc. Natl. Acad. Sci. USA* 88:4363-66; Hoogenboom et al., 1992 *J. Molec. Biol.* 227:381-388; Schlebusch et al., 1997 *Hybridoma* 16:47-52 and references cited therein. For example, a library containing a plurality of polynucleotide sequences encoding Ig variable region fragments may be inserted into the genome of a filamentous bacteriophage, such as M13 or a variant  
25 thereof, in frame with the sequence encoding a phage coat protein, for instance, gene III or gene VIII of M13, to create an M13 fusion protein. A fusion protein may be a fusion of the coat protein with the light chain variable region domain and/or with the heavy chain variable region domain.

According to certain embodiments, immunoglobulin Fab fragments may  
30 also be displayed on the phage particle, as follows. Polynucleotide sequences encoding Ig constant region domains may be inserted into the phage genome in frame with a coat



protein. The phage coat fusion protein may thus be fused to an Ig light chain or heavy chain fragment (Fd). For example, from a human Ig library, the polynucleotide sequence encoding the human kappa constant region may be inserted into a vector in frame with the sequence encoding at least one of the phage coat proteins. Additionally  
5 or alternatively, the polynucleotide sequence encoding the human IgG1 CH1 domain may be inserted in frame with the sequence encoding at least one other of the phage coat proteins. A plurality of polynucleotide sequences encoding variable region domains (*e.g.*, derived from a DNA library) may then be inserted into the vector in frame with the constant region-coat protein fusions, for expression of Fab fragments  
10 fused to a bacteriophage coat protein.

Phage that display an Ig fragment (*e.g.*, an Ig V-region or Fab) that binds to a PTP polypeptide may be selected by mixing the phage library with PTP or a variant or a fragment thereof, or by contacting the phage library with a PTP polypeptide immobilized on a solid matrix under conditions and for a time sufficient to allow  
15 binding. Unbound phage are removed by a wash, which typically may be a buffer containing salt (*e.g.*, NaCl) at a low concentration, preferably with less than 100 mM NaCl, more preferably with less than 50 mM NaCl, most preferably with less than 10 mM NaCl, or, alternatively, a buffer containing no salt. Specifically bound phage are then eluted with an NaCl-containing buffer, for example, by increasing the salt  
20 concentration in a step-wise manner. Typically, phage that bind the PTP with higher affinity will require higher salt concentrations to be released. Eluted phage may be propagated in an appropriate bacterial host, and generally, successive rounds of PTP binding and elution can be repeated to increase the yield of phage expressing PTP-specific immunoglobulin. Combinatorial phage libraries may also be used for  
25 humanization of non-human variable regions. *See, e.g.*, Rosok et al., 1996 *J. Biol. Chem.* 271:22611-18; Rader et al., 1998 *Proc. Natl. Acad. Sci. USA* 95:8910-15. The DNA sequence of the inserted immunoglobulin gene in the phage so selected may be determined by standard techniques. *See*, Sambrook et al., 1989 *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press. The affinity selected Ig-encoding  
30 sequence may then be cloned into another suitable vector for expression of the Ig

fragment or, optionally, may be cloned into a vector containing Ig constant regions, for expression of whole immunoglobulin chains.

Phage display techniques may also be used to select polypeptides, peptides or single chain antibodies that bind to PTP. For examples of suitable vectors  
5 having multicloning sites into which candidate nucleic acid molecules (*e.g.*, DNA) encoding such peptides or antibodies may be inserted, *see, e.g.*, McLafferty et al., *Gene* 128:29-36, 1993; Scott et al., 1990 *Science* 249:386-390; Smith et al., 1993 *Methods Enzymol.* 217:228-257; Fisch et al., 1996, *Proc. Natl. Acad. Sci. USA* 93:7761-66. The inserted DNA molecules may comprise randomly generated sequences, or may encode  
10 variants of a known peptide or polypeptide domain that specifically binds to a PTP polypeptide, or variant or fragment thereof, as provided herein. Generally, the nucleic acid insert encodes a peptide of up to 60 amino acids, more preferably a peptide of 3 to 35 amino acids, and still more preferably a peptide of 6 to 20 amino acids. The peptide encoded by the inserted sequence is displayed on the surface of the bacteriophage.  
15 Phage expressing a binding domain for a PTP polypeptide may be selected on the basis of specific binding to an immobilized PTP polypeptide as described above. As provided herein, well-known recombinant genetic techniques may be used to construct fusion proteins containing the fragment thereof. For example, a polypeptide may be generated that comprises a tandem array of two or more similar or dissimilar affinity  
20 selected PTP binding peptide domains, in order to maximize binding affinity for PTP of the resulting product.

In certain other embodiments, the invention contemplates PTP-specific antibodies that are multimeric antibody fragments. Useful methodologies are described generally, for example in Hayden et al. 1997, *Curr Opin. Immunol.* 9:201-12; Coloma  
25 et al., 1997 *Nat. Biotechnol.* 15:159-63). For example, multimeric antibody fragments may be created by phage techniques to form miniantibodies (U.S. Patent No. 5,910 573) or diabodies (Holliger et al., 1997, *Cancer Immunol. Immunother.* 45:128-130). Multimeric fragments may be generated that are multimers of a PTP-specific Fv, or that are bispecific antibodies comprising a PTP-specific Fv noncovalently associated with a  
30 second Fv having a different antigen specificity. *See, e.g.*, Koelemij et al., 1999 *J. Immunother.* 22:514-24. As another example, a multimeric antibody may comprise a

bispecific antibody having two single chain antibodies or Fab fragments. According to certain related embodiments, a first Ig fragment may be specific for a first antigenic determinant on a PTP polypeptide (or variant or fragment thereof), while a second Ig fragment may be specific for a second antigenic determinant of the PTP polypeptide.

5 Alternatively, in certain other related embodiments, a first immunoglobulin fragment may be specific for an antigenic determinant on a PTP polypeptide or variant or fragment thereof, and a second immunoglobulin fragment may be specific for an antigenic determinant on a second, distinct (*i.e.*, non-PTP) molecule. Also contemplated are bispecific antibodies that specifically bind PTP, wherein at least one

10 antigen-binding domain is present as a fusion protein.

Introducing amino acid mutations into PTP-binding immunoglobulin molecules may be useful to increase the specificity or affinity for PTP, or to alter an effector function. Immunoglobulins with higher affinity for PTP may be generated by site-directed mutagenesis of particular residues. Computer assisted three-dimensional

15 molecular modeling may be employed to identify the amino acid residues to be changed, in order to improve affinity for the PTP polypeptide. *See, e.g.*, Mountain et al., 1992, *Biotechnol. Genet. Eng. Rev.* 10: 1-142. Alternatively, combinatorial libraries of CDRs may be generated in M13 phage and screened for immunoglobulin fragments with improved affinity. *See, e.g.*, Glaser et al., 1992, *J. Immunol.* 149:3903-

20 3913; Barbas et al., 1994 *Proc. Natl. Acad. Sci. USA* 91:3809-13; U.S. Patent No. 5,792, 456).

Effector functions may also be altered by site-directed mutagenesis. *See, e.g.*, Duncan et al., 1988 *Nature* 332:563-64; Morgan et al., 1995 *Immunology* 86:319-24; Eghtedarzede-Kondri et al., 1997 *Biotechniques* 23:830-34. For example,

25 mutation of the glycosylation site on the Fc portion of the immunoglobulin may alter the ability of the immunoglobulin to fix complement. *See, e.g.*, Wright et al., 1997 *Trends Biotechnol.* 15:26-32. Other mutations in the constant region domains may alter the ability of the immunoglobulin to fix complement, or to effect antibody-dependent cellular cytotoxicity. *See, e.g.*, Duncan et al., 1988 *Nature* 332:563-64; Morgan et al.,

30 1995 *Immunology* 86:319-24; Sensel et al., 1997 *Mol. Immunol.* 34:1019-29.

The nucleic acid molecules encoding an antibody or fragment thereof that specifically binds PTP, as described herein, may be propagated and expressed according to any of a variety of well-known procedures for nucleic acid excision, ligation, transformation and transfection. Thus, in certain embodiments expression of an antibody fragment may be preferred in a prokaryotic host, such as *Escherichia coli* (see, e.g., Pluckthun et al., 1989 *Methods Enzymol.* 178:497-515). In certain other embodiments, expression of the antibody or a fragment thereof may be preferred in a eukaryotic host cell, including yeast (e.g., *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, and *Pichia pastoris*), animal cells (including mammalian cells) or plant cells. Examples of suitable animal cells include, but are not limited to, myeloma, COS, CHO, or hybridoma cells. Examples of plant cells include tobacco, corn, soybean, and rice cells. By methods known to those having ordinary skill in the art and based on the present disclosure, a nucleic acid vector may be designed for expressing foreign sequences in a particular host system, and then polynucleotide sequences encoding the PTP binding antibody (or fragment thereof) may be inserted. The regulatory elements will vary according to the particular host.

A PTP-binding immunoglobulin (or fragment thereof) as described herein may contain a detectable moiety or label such as an enzyme, cytotoxic agent or other reporter molecule, including a dye, radionuclide, luminescent group, fluorescent group, or biotin, or the like. The PTP-specific immunoglobulin or fragment thereof may be radiolabeled for diagnostic or therapeutic applications. Techniques for radiolabeling of antibodies are known in the art. See, e.g., Adams 1998 *In Vivo* 12:11-21; Hiltunen 1993 *Acta Oncol.* 32:831-9. Therapeutic applications are described in greater detail below and may include use of the PTP-binding antibody (or fragment thereof) in conjunction with other therapeutic agents. The antibody or fragment may also be conjugated to a cytotoxic agent as known in the art and provided herein, for example, a toxin, such as a ribosome-inactivating protein, a chemotherapeutic agent, an anti-mitotic agent, an antibiotic or the like.

As provided herein and according to methodologies well known in the art, polyclonal and monoclonal antibodies may be used for the affinity isolation of PTP polypeptides. See, e.g., Hermanson et al., *Immobilized Affinity Ligand Techniques*,

Academic Press, Inc. New York, 1992. Briefly, an antibody (or antigen-binding fragment thereof) may be immobilized on a solid support material, which is then contacted with a sample comprising the polypeptide of interest (e.g., a PTP). Following separation from the remainder of the sample, the polypeptide is then released from the  
5 immobilized antibody.

#### METHODS FOR DETECTING PTP EXPRESSION

Certain embodiments of the present invention provide methods that employ antibodies raised against PTP for assay purposes. Certain assays involve using  
10 an antibody or other agent to detect the presence or absence of PTP, or proteolytic fragments thereof. Assays may generally be performed using any of a variety of samples obtained from a biological source, as provided herein.

To detect a PTP protein, the reagent is typically an antibody, as provided herein. There are a variety of assay formats known to those having ordinary skill in the  
15 art for using an antibody to detect a polypeptide in a sample. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. For example, the assay may be performed in a Western blot format, wherein a protein preparation from the biological sample is resolved by gel electrophoresis, transferred to a suitable membrane and allowed to react with the antibody. The presence of the  
20 antibody on the membrane may then be detected using a suitable detection reagent, as described below. In certain embodiments of the present invention, this format may be preferred to determine, establish or confirm the specific identity of a PTP that is identified as being reversibly modified or reversibly oxidized in a cell.

In another embodiment, isolation of a PTP may involve the use of  
25 antibody immobilized on a solid support to bind to the target PTP and remove it from the remainder of the sample. The bound PTP may then be detected using a second antibody or reagent that contains a reporter group. Alternatively, a competitive assay may be utilized, in which a PTP polypeptide is labeled with a reporter group and allowed to bind to the immobilized antibody after incubation of the antibody with the  
30 sample. The extent to which components of the sample inhibit the binding of the

labeled polypeptide to the antibody is indicative of the reactivity of the sample with the immobilized antibody, and as a result, indicative of the level of PTP in the sample.

The solid support may be any material known to those having ordinary skill in the art to which the antibody may be attached, such as a test well in a microtiter plate, a nitrocellulose filter or another suitable membrane. Alternatively, the support  
5 may be a bead or disc, such as glass, fiberglass, latex or a plastic such as polystyrene or polyvinylchloride. The antibody may be immobilized on the solid support using a variety of techniques known to those in the art, which are amply described in the patent and scientific literature.

10 In certain embodiments, the assay for detection of PTP in a sample is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the biological sample, such that PTP within the sample is allowed to bind to the immobilized antibody (a 30 minute incubation time at room temperature  
15 is generally sufficient). Unbound sample is then removed from the immobilized PTP/antibody complexes and a second antibody (containing a reporter group such as an enzyme, dye, radionuclide, luminescent group, fluorescent group or biotin) capable of binding to a different site on the PTP is added. The amount of second antibody that remains bound to the solid support is then determined using a method appropriate for  
20 the specific reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected  
25 by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products. Standards and standard additions may be used to determine the level of PTP in a sample, using well known techniques.

In a related aspect of the present invention, kits for detecting a reversibly  
30 modified PTP, and for determining PTP phosphatase activity, are provided. Such kits may be designed for detecting the level of PTP, or may detect phosphatase activity of

PTP in a direct phosphatase assay or a coupled phosphatase assay. In general, the kits of the present invention comprise one or more containers enclosing elements, such as reagents or buffers, to be used in the assay. A kit for detecting the level of a PTP typically contains a reagent that specifically binds to the PTP protein; the reagent is typically an antibody. Such kits also contain a reporter group suitable for direct or indirect detection of the reagent (*i.e.*, the reporter group may be covalently bound to the reagent or may be bound to a second molecule, such as Protein A, Protein G, immunoglobulin or lectin, which is itself capable of binding to the reagent). Suitable reporter groups include, but are not limited to, enzymes (*e.g.*, horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. Such reporter groups may be used to directly or indirectly detect binding of the reagent to a sample component using standard methods known to those having ordinary skill in the art.

Kits for detecting PTP activity typically comprise a PTP substrate in combination with a suitable buffer. PTP activity may be specifically detected by performing an immunoprecipitation step with a PTP-specific antibody prior to performing a phosphatase assay as described above. Other reagents for use in detecting dephosphorylation of substrate may also be provided.

## 20 SCREENING ASSAYS FOR AGENTS

Where a PTP is identified that is a reversibly modified/ oxidized component of a biological signaling pathway as provided herein, by using the methods of the present invention, it is further contemplated that in certain further embodiments the invention provides a screening assay for an agent that alters an inducible biological signaling pathway. According to such assays, a cell comprising the PTP (and hence the inducible pathway wherein the PTP is reversibly modified) is contacted with a stimulus that induces the pathway in the absence and presence of a candidate agent, under conditions permissive for induction of the pathway by the stimulus. PTPs are then isolated from the cell in the presence of a sulfhydryl-reactive agent that is capable of covalently (*e.g.*, irreversibly) modifying a sulfhydryl group of the PTP active site invariant cysteine where, as described herein, the signaling pathway component PTP

that is reversibly modified (*e.g.*, oxidized) is protected from inactivation by such sulfhydryl agent, and PTP catalytic activity is determined by any of a variety of established methods, as also provided herein, after the reversibly modified PTP is reactivated by reversal of the modification (*e.g.*, under reducing conditions). Decreased  
5 substrate dephosphorylation when the pathway is induced in the presence of the candidate agent, relative to the level of dephosphorylation when induction transpires in the absence of the candidate agent, indicates that the agent is an inhibitor or antagonist (*e.g.*, results in PTP catalytic activity in the cell that is decreased in a statistically significant manner) of the reversibly modified PTP. Conversely, increased substrate  
10 dephosphorylation when the pathway is induced in the presence of the candidate agent, relative to the level of dephosphorylation when induction transpires in the absence of the candidate agent, indicates that the agent is a potentiator or agonist (*i.e.*, an activity enhancer) of the reversibly modified PTP (*e.g.*, results in PTP catalytic activity in the cell that is increased in a statistically significant manner). The assays of this  
15 embodiment of the invention therefore provide a method for identifying an agent that alters an inducible biological signaling pathway, which agent will be useful where specific manipulation of or intervention in a particular stimulus-inducible pathway may be desirable.

Candidate agents for use in a method for identifying an agent that alters  
20 (*e.g.*, increases or decreases in a statistically significant manner at least one phenotype associated with pathway induction) an inducible biological signaling pathway according to the present invention may be provided as "libraries" or collections of compounds, compositions or molecules. Such molecules typically include compounds known in the art as "small molecules" and having molecular weights less than  $10^5$  daltons, preferably  
25 less than  $10^4$  daltons and still more preferably less than  $10^3$  daltons. For example, members of a library of test compounds can be administered to a plurality of samples, each containing at least one biological sample comprising a cell that comprises a PTP which has been identified as a reversibly modified (*e.g.*, oxidized) component of an inducible biological signaling pathway as provided herein, and then assayed for their  
30 ability to enhance or inhibit dephosphorylation of a PTP substrate by the PTP. Compounds so identified as capable of influencing PTP function (*e.g.*, phosphotyrosine



and/or phosphoserine/threonine dephosphorylation) are valuable for therapeutic and/or diagnostic purposes, since they permit treatment and/or detection of diseases associated with PTP activity. Such compounds are also valuable in research directed to molecular signaling mechanisms that involve PTP, and to refinements in the discovery and  
5 development of future PTP compounds exhibiting greater specificity.

Candidate agents further may be provided as members of a combinatorial library, which preferably includes synthetic agents prepared according to a plurality of predetermined chemical reactions performed in a plurality of reaction vessels. For example, various starting compounds may be prepared employing one or  
10 more of solid-phase synthesis, recorded random mix methodologies and recorded reaction split techniques that permit a given constituent to traceably undergo a plurality of permutations and/or combinations of reaction conditions. The resulting products comprise a library that can be screened followed by iterative selection and synthesis procedures, such as a synthetic combinatorial library of peptides (see *e.g.*,  
15 PCT/US91/08694, PCT/US91/04666, which are hereby incorporated by reference in their entireties) or other compositions that may include small molecules as provided herein (see *e.g.*, PCT/US94/08542, EP 0774464, U.S. 5,798,035, U.S. 5,789,172, U.S. 5,751,629, which are hereby incorporated by reference in their entireties). Those having ordinary skill in the art will appreciate that a diverse assortment of such libraries  
20 may be prepared according to established procedures, and tested using PTP according to the present disclosure.

#### THERAPEUTIC METHODS

One or more agents capable of altering an inducible biological signaling pathway and identified according to the above described methods may also be used to  
25 modulate (*e.g.*, inhibit or potentiate) PTP activity in a patient. As used herein, a "patient" may be any mammal, including a human, and may be afflicted with a condition associated with PTP activity or may be free of detectable disease. Accordingly, the treatment may be of an existing disease or may be prophylactic. Conditions associated with PTP activity include any disorder associated with cell  
30 proliferation, including cancer, graft-versus-host disease (GVHD), autoimmune

diseases, allergy or other conditions in which immunosuppression may be involved, metabolic diseases, abnormal cell growth or proliferation and cell cycle abnormalities.

For administration to a patient, one or more modulating agents are generally formulated as a pharmaceutical composition. A pharmaceutical composition  
5 may be a sterile aqueous or non-aqueous solution, suspension or emulsion, which additionally comprises a physiologically acceptable carrier (*i.e.*, a non-toxic material that does not interfere with the activity of the active ingredient). Such compositions may be in the form of a solid, liquid or gas (aerosol). Alternatively, compositions of the present invention may be formulated as a lyophilizate or compounds may be  
10 encapsulated within liposomes using well known technology. Pharmaceutical compositions within the scope of the present invention may also contain other components, which may be biologically active or inactive. Such components include, but are not limited to, buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins,  
15 polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, stabilizers, dyes, flavoring agents, and suspending agents and/or preservatives.

Any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of the present invention. Carriers for  
20 therapeutic use are well known, and are described, for example, in *Remingtons Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro ed. 1985). In general, the type of carrier is selected based on the mode of administration. Pharmaceutical compositions may be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, intrathecal, rectal, vaginal, sublingual or  
25 parenteral administration, including subcutaneous, intravenous, intramuscular, intrasternal, intracavernous, intrameatal or intraurethral injection or infusion. For parenteral administration, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum,  
30 cellulose, kaolin, glycerin, starch dextrins, sodium alginate, carboxymethylcellulose, ethyl cellulose, glucose, sucrose and/or magnesium carbonate, may be employed.

A pharmaceutical composition (*e.g.*, for oral administration or delivery by injection) may be in the form of a liquid (*e.g.*, an elixir, syrup, solution, emulsion or suspension). A liquid pharmaceutical composition may include, for example, one or more of the following: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. A parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. The use of physiological saline is preferred, and an injectable pharmaceutical composition is preferably sterile.

The compositions described herein may be formulated for sustained release (*i.e.*, a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such compositions may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain an agent dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Within a pharmaceutical composition, a PTP modulating agent may be linked to any of a variety of compounds. For example, such an agent may be linked to a targeting moiety (*e.g.*, a monoclonal or polyclonal antibody, a protein or a liposome) that facilitates the delivery of the agent to the target site. As used herein, a "targeting moiety" may be any substance (such as a compound or cell) that, when linked to an

agent enhances the transport of the agent to a target cell or tissue, thereby increasing the local concentration of the agent. Targeting moieties include antibodies or fragments thereof, receptors, ligands and other molecules that bind to cells of, or in the vicinity of, the target tissue. An antibody targeting agent may be an intact (whole) molecule, a  
5 fragment thereof, or a functional equivalent thereof. Examples of antibody fragments are F(ab')<sub>2</sub>, -Fab', Fab and F[v] fragments, which may be produced by conventional methods or by genetic or protein engineering. Linkage is generally covalent and may be achieved by, for example, direct condensation or other reactions, or by way of bi- or multi-functional linkers. Targeting moieties may be selected based on the cell(s) or  
10 tissue(s) toward which the agent is expected to exert a therapeutic benefit.

Pharmaceutical compositions may be administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dosage and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular  
15 form of the active ingredient and the method of administration. In general, an appropriate dosage and treatment regimen provides the agent(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival). For prophylactic use, a dose should be sufficient to prevent, delay the  
20 onset of or diminish the severity of a disease associated with cell proliferation.

Optimal dosages may generally be determined using experimental models and/or clinical trials. In general, the amount of polypeptide present in a dose, or produced *in situ* by DNA present in a dose, ranges from about 0.01 µg to about 100 µg per kg of host, typically from about 0.1 µg to about 10 µg. The use of the minimum  
25 dosage that is sufficient to provide effective therapy is usually preferred. Patients may generally be monitored for therapeutic or prophylactic effectiveness using assays suitable for the condition being treated or prevented, which will be familiar to those having ordinary skill in the art. Suitable dose sizes will vary with the size of the patient, but will typically range from about 10 mL to about 500 mL for 10-60 kg  
30 animal.

The following Examples are offered for the purpose of illustrating the present invention and are not to be construed to limit the scope of this invention.

## EXAMPLES

## EXAMPLE 1

## REVERSIBLE INACTIVATION OF PTPs IN RAT-1 CELLS BY HYDROGEN PEROXIDE

5

Cell culture, transient transfection, immunoprecipitation and immunoblotting: Rat-1 fibroblasts (American Type Culture Collection, Manassas, VA) were routinely maintained in DMEM supplemented with 10% FBS, 1% glutamine, 100 U/ml penicillin and 100 µg/ml streptomycin (all reagents Sigma, St. Louis, MO, unless  
10 otherwise noted). For stimulation with H<sub>2</sub>O<sub>2</sub> and peptide growth factors, cells were plated in media containing 10% FBS for 48 hours, then serum-starved for 16 hours before treatment. For transient transfection, Rat-1 cells were plated in DMEM medium supplemented with 10% FBS, for 16 hours. The culture medium was replaced by OptiMEM™ (Invitrogen Life Technologies, Inc. Gaithersburg, MD) without serum,  
15 then plasmid (5 µg/dish) was introduced into cells by LipofectAMINE™ and PLUS™ reagents (Life Technologies), according to the manufacture's recommendations. The transfection efficiency was routinely 40%.

For immunoprecipitation, cells were rinsed with ice-cold PBS, then lysed in ice-cold 20 mM Hepes (pH 7.5), 1% NP-40, 150 mM NaCl, 10% glycerol, 200  
20 µM Na<sub>3</sub>VO<sub>5</sub> and protease inhibitors (25 µg/ml of aprotinin and leupeptin). Antibodies having the indicated specificities were purchased from the following suppliers: SHP-1 (C-19), SHP-2 (C-18) and PI3K (Z-8), Santa Cruz Biotechnology, Santa Cruz, CA; phospho-MAPK and MAPK, Cell Signaling, Inc. (Beverly, MA); GAP, BD Transduction Laboratories (Lexington, KY); and pTyr mAb PT66, Sigma, St. Louis,  
25 MO. The anti-pTyr antibody G104 was described previously (Garton et al., 1997 *Oncogene* 15, 877-885). Anti-PDGFRβ antibody (Ab-X) was a gift from Dr. Daniel DiMaio at Yale University (Irusta and DiMaio, 1998 *EMBO J* 17, 6912-6923). Anti-human G-CSF receptor (G-CSFR) antibody was provided by Dr. Toshio Hirano at Osaka University, Japan (Fukada et al., 1996 *Immunity* 5, 449-460). Lysate (400 µg)  
30 was incubated with 5 µg of antibody conjugated to protein A/G-Sepharose (Amersham Pharmacia, Arlington Heights, IL) for 2 hours at 4 °C. For immunoblotting, aliquots of

total lysates (30 µg per sample) or immunoprecipitates were subjected to SDS-PAGE and transferred to nitrocellulose filters, which were incubated with appropriate primary and secondary antibodies and the specific signals were visualized by the ECL detection system (Amersham Pharmacia).

5                   To determine whether ROS stimulated intracellular tyrosine phosphorylation through the oxidation and inhibition of cellular PTPs, a modified in-gel PTP activity assay was devised, as follows: As substrate, poly (4:1) Glu-Tyr (Sigma) was labeled with [ $\gamma$ - $^{32}$ P]-ATP using the GST-FER fusion PTK, as described previously (Shen et al., 1998 *J. Biol. Chem.* 273:6474-81). The labeled substrates were used  
10 within three weeks to limit the variation of its specific activity from experiment to experiment. The lysis buffer (25 mM CH<sub>3</sub>COONa, 1% NP-40, 150 mM NaCl, 10% glycerol, pH 5.5) was degassed at 4 °C for overnight, before catalase and superoxide dismutase (both 100 µg/ml), protease inhibitors and 10 mM iodoacetic acid (IAA) were added. Following stimulation, cells were lysed under anaerobic conditions in an argon  
15 chamber. Lysates (25 µg) were processed as described herein and an “in-gel” phosphatase assay (Burridge and Nelson, 1995) was conducted using SDS-PAGE gels containing a radioactively-labeled substrate ( $1.5 \times 10^6$  cpm/20 ml gel solution, approximately 2 µM p-Tyr).

Cells were triggered with the appropriate stimulus and harvested under  
20 anaerobic conditions in lysis buffer containing IAA. Those PTPs that had not encountered ROS in the cell became irreversibly inactivated by alkylation of their active site Cys with IAA. However, in contrast, any PTPs in which the active site Cys had been oxidized in response to the stimulus were resistant to alkylation. For the “in-gel” phosphatase assay, a 10% SDS-PAGE gel was cast containing a radioactively-  
25 labeled substrate. An aliquot of cell lysate was subjected to SDS-PAGE and proteins in the gel were sequentially denatured, then renatured in the presence of reducing reagents. Under these conditions, the activity of the PTPs in which the active site Cys had been subjected to stimulus-dependent oxidation to sulfenic acid was recovered, whereas those that were not oxidized in response to the initial stimulus, and were irreversibly  
30 alkylated in the lysis step, remained inactive. The reaction was then terminated by fixing, staining and destaining the gel. Finally the gel was dried and exposed to film.

The presence of a PTP was visualized by substrate dephosphorylation, as the appearance of a clear, white area on the black background of labeled substrate. As shown in Fig. 1, the PTPs that exhibited catalytic phosphatase activity in this assay would be those originally protected from post-lysis alkylation by a stimulus-dependent  
5 modification at the active site Cys, which was reversed by DTT, consistent with oxidation of the Cys to sulfenic acid.

The data shown in Fig. 2A illustrate that iodoacetic acid (IAA) in the lysis buffer effectively inactivated PTPs in a lysate of Rat-1 cells (lane 2, compared to lane 1), via irreversible alkylation of the invariant, active site Cys residue of these  
10 enzymes (Zhang and Dixon, 1993 *Biochemistry* 32:9340-45). Fig. 2A shows the results when serum-deprived Rat-1 cells were exposed to various concentrations of  $H_2O_2$  for 1 min, harvested and lysed in the absence (lane 1) or presence (lanes 2-7) of 10 mM IAA. Aliquots of lysate were subjected to the in-gel PTP assay. When  $H_2O_2$  was added to the culture media, it gained rapid access to the intracellular environment and within 1  
15 minute the active site Cys residue of various PTPs was oxidized, thereby protecting them from alkylation by IAA (lanes 3 - 7, Fig. 2A). Furthermore, 200  $\mu M$   $H_2O_2$  was sufficient to oxidize all of the PTPs detectable in this assay format, but more extensive oxidation occurred at higher concentrations of  $H_2O_2$  (Fig. 2A).

Fig. 2B shows results obtained when tyrosine phosphorylated proteins  
20 were immunoprecipitated from lysates of  $H_2O_2$ -treated cells with Ab PT-66, then immunoblotted with anti-pTyr Ab (G104). The tyrosine phosphorylation of proteins of ~120 kDa and 70 kDa was induced in a dose-dependent fashion coincident with exposure of cells to  $H_2O_2$  (Fig. 2B), suggesting a link between oxidation/inhibition of PTPs and enhanced tyrosine phosphorylation in Rat-1 cells. This stimulation also  
25 triggered the phosphorylation of ERK MAP kinases (MAPKs). N-acetyl cysteine (NAC), a widely used ROS scavenger, blocked PTP oxidation and inactivation induced by 200  $\mu M$   $H_2O_2$ , thus confirming that the effects on PTP activity shown in the in-gel assay were due to  $H_2O_2$ -induced intracellular oxidation (Fig. 2C). Fig. 2C depicts the results obtained when cells were preincubated in the absence or presence of 30 mM  
30 NAC for 40 minutes and excess NAC removed by two washes with fresh culture medium, after which the Rat-1 cells were exposed to 200  $\mu M$   $H_2O_2$  and lysed in the



presence of 10 mM IAA at the indicated times. Lysates were subjected to the in-gel PTP assay.

In addition, depletion of the cellular pool of glutathione (GSH) by exposure of the cells to L-buthionine-SR-sulfoximine (BSO), a specific inhibitor of  $\gamma$ -glutamylcysteine synthetase, markedly attenuated the recovery of PTP activity following removal of an  $H_2O_2$  stimulus (Fig. 2D). To obtain the data presented in Fig. 2D, Rat-1 cells were serum-starved in the absence or presence of 2.5 mM BSO for 16 h.  $H_2O_2$  (200  $\mu$ M) was added for 2 minutes, then removed by washing the cells with fresh culture media. Incubation was then continued until harvesting in lysis buffer containing 10 mM IAA at the times indicated. Oxidized PTPs were visualized by the in-gel phosphatase activity assay. Arrows indicate PTPs for which reduction/reactivation exhibited dependence on intracellular GSH. Stimulation with  $H_2O_2$  led to oxidation of several PTPs (lane 2), which were quickly reduced once  $H_2O_2$  was removed (Fig. 2D, lanes 3-6). Recovery was essentially complete within 10-20 minutes of removal of  $H_2O_2$ . However, when the same analysis was performed on Rat-1 cells that had been subjected to pretreatment with BSO, oxidation persisted even 30 minutes after removal of  $H_2O_2$  (Fig. 2D lanes 8-12). Surprisingly, these observations provide the first demonstration that multiple PTPs may be oxidized and inactivated by ROS in a cellular environment.

## EXAMPLE 2

### $H_2O_2$ -INDUCED MITOGENIC SIGNALING ASSOCIATED WITH PTP INACTIVATION

In order to explore the importance of oxidation and inhibition of PTP function for ROS-induced mitogenesis, the effects of  $H_2O_2$  and the synthetic ROS t-butyl hydroperoxide (t-BHP) were tested. Initially, the susceptibility of an activated mutant form of SHP-2 (E76A) to alkylation by IAA was compared following treatment with either  $H_2O_2$  or t-BHP. Using the modified in-gel PTP assay described in Example 1, SHP-2, which had been pre-treated with PBS, was inactivated by IAA (lane 2, compared to lane 1, Fig. 3A), whereas oxidation with  $H_2O_2$  protected SHP-2 from alkylation (Fig. 3A). Briefly, purified SHP-2 (E76A mutant) was incubated with PBS,

H<sub>2</sub>O<sub>2</sub> or t-BHP at 37 °C for 5 mins. Aliquots were then incubated at room temp for a further 5 minutes, either in the absence (- IAA) or presence (+IAA) of 4 mM IAA, and subjected to the in-gel PTP activity assay (1 ng SHP-2/lane). Even at 2 mM H<sub>2</sub>O<sub>2</sub>, SHP-2 was not irreversibly oxidized since its activity was recovered in the in-gel assay (Fig. 3A). In contrast, t-BHP was unable to oxidize and inactivate SHP-2 *in vitro* and thus did not protect the invariant Cys residue of SHP-2 from alkylation (Fig. 3A).

The effects of H<sub>2</sub>O<sub>2</sub> and t-BHP on inactivation of PTPs and activation of MAPK signaling pathways were next compared in a cellular context. Intracellular ROS were measured using 2',7'-dichlorofluorescein diacetate (H<sub>2</sub>DCFDA) and 5-(and-6)-chloromethyl-2',7'-dichlorodihydrofluorescein diacetate (CM-H<sub>2</sub>DCFDA) (all fluorescent ROS indicators from Molecular Probes, Eugene, OR) either by fluorescence microscopy, using a Zeiss Axiovert 405M inverted microscope equipped with a fluorescence attachment and digital camera, or by cell sorting, using a FACSCalibur System (Coulter Instruments, Hialeah, FL), according to the manufacturer's recommendations. Rat-1 cells were pre-loaded with 20 μM H<sub>2</sub>DCFDA in the dark for 20 mins, then exposed to H<sub>2</sub>O<sub>2</sub> and t-BHP (both 200 μM) for 5 mins. Images of ROS-induced DCF fluorescence are shown at magnification 400X (Fig. 3B upper panel). Cells (1 x 10<sup>5</sup>) that underwent the same treatment as above were harvested and resuspended in Hanks' solution, then immediately subjected to flow cytometric analysis to measure ROS-induced DCF fluorescence. The basal peak indicates background fluorescence, whereas the rightward shifted peak indicates ROS-induced DCF fluorescence (Fig. 3B, lower panels). Initially, fluorescence microscopy of Rat-1 cells, preloaded with H<sub>2</sub>DCFDA, showed that treatment with either H<sub>2</sub>O<sub>2</sub> or t-BHP led to rapid oxidation and the appearance of the fluorescent derivative, DCF (upper panels, Fig. 3B). Furthermore, upon flow cytometric analysis no quantitative difference was observed between the H<sub>2</sub>O<sub>2</sub>- and t-BHP-induced shift of fluorescence (Fig. 3B, lower panels). However, when the ability to oxidize PTPs in the cells was examined, reproducible inactivation of PTPs was detected in response to H<sub>2</sub>O<sub>2</sub> but not in response to t-BHP (Fig. 3C). Cells were exposed to H<sub>2</sub>O<sub>2</sub> and t-BHP (each at 200 μM) for the indicated times, lysed in the presence of 10 mM IAA and oxidized PTPs were visualized in the in-gel PTP activity assay.

H<sub>2</sub>O<sub>2</sub> and t-BHP were next compared for their effects on tyrosine phosphorylation of cellular proteins, and on activation of MAPKs. As shown in Fig. 3D, after exposure to H<sub>2</sub>O<sub>2</sub> and t-BHP (each at 200  $\mu$ M), lysates were prepared and pTyr proteins were immunoprecipitated with Ab PT-66, then immunoblotted with anti-pTyr Ab G104 (Fig. 3D, upper panel). An aliquot of lysate from each treatment group was immunoblotted with anti-phospho-MAPK Ab and subsequently with anti-MAPK Ab (Fig. 3D, lower panel). As shown in Fig. 3D, the inactivation of PTPs by H<sub>2</sub>O<sub>2</sub> was associated with enhanced tyrosine phosphorylation and mitogenic signaling. In contrast, t-BHP elicited less pronounced effects on tyrosine phosphorylation and was unable to activate MAPKs (Fig. 3D), presumably due to its inability to oxidize and inactivate the PTPs. Without wishing to be bound by theory, these results are consistent with a role of PTP inactivation in the mitogenic effects of ROS.

15

## EXAMPLE 3

OXIDATION OF A 70 KDA PTP ASSOCIATED WITH PDGF-INDUCED MITOGENIC  
SIGNALING IN RAT-1 CELLS AND IDENTIFICATION OF THE 70 KDA PTP AS SHP-2

As described above, treatment of Rat-1 cells with H<sub>2</sub>O<sub>2</sub> led to inactivation of multiple PTPs (Figs. 2-3). This Example describes studies to determine whether the production of ROS in response to physiological stimuli also resulted in oxidation and inactivation of members of the PTP family, and whether there was specificity in the response. Initially examined were the effects of PDGF, a peptide growth factor, which has been shown to produce ROS in various cell types (Bae et al., 2000; Sundaresan et al., 1995). Preliminary experiments showed that treatment of Rat-1 cells with PDGF resulted in a rapid increase in the tyrosine phosphorylation of cellular proteins and the enhanced phosphorylation of MAPKs. Lysates of PDGF-stimulated Rat-1 cells were then analyzed using the modified in-gel PTP activity assay described above. The results, as shown in Figure 4, demonstrated that PDGF stimulation induced a rapid and transient oxidation of a PTP having an apparent molecular mass of ~70 kDa. Serum-starved Rat-1 cells were exposed to 50 ng/ml

PDGF-BB for the times indicated (Fig. 4A). Lysates were prepared in the presence of 10 mM IAA and subjected to the in-gel PTP assay. The arrow indicates a 70k PTP that was transiently oxidized following stimulation of Rat-1 cells with PDGF. The result shown is representative of four independent experiments. Oxidation of this 70 kDa PTP was reversible, reaching a maximum at 5 minutes, followed by marked reduction, almost to basal levels, within 20 minutes of PDGF treatment (Fig. 4A).

A possible role of oxidation/inactivation of the 70k PTP in regulating PDGFR-mediated signaling was next investigated by testing the effects of the antioxidant NAC. Cells were incubated for 40 minutes in the presence or absence of 30 mM NAC prior to PDGF stimulation. Excess NAC was removed prior to addition of PDGF (50 ng/ml). PDGF-induced oxidation of the 70k PTP, which was impaired in the presence of NAC (Fig. 4B, arrow), was visualized by the modified in-gel PTP assay. Then the modified in-gel PTP assay was used to examine the effects of the growth factor on the activity of the 70k PTP. When the levels of PDGF-induced ROS were reduced by pretreatment with NAC, oxidation of the 70k PTP was markedly attenuated (Fig. 4B). Furthermore, the ligand-induced tyrosine phosphorylation of the PDGFR was greatly diminished, and the activation of MAPKs was completely eliminated, in NAC-treated cells (Fig. 4C). Cells were treated with NAC and PDGF as described above. PDGFR was immunoprecipitated from lysates with Ab-X and immunoblotted with anti-pTyr Ab G104. The same filter was subsequently re-probed with Ab-X (Fig. 4C, upper panels). Aliquots of cell lysate from each treatment were immunoblotted with anti-phospho-MAPK Ab and re-probed with anti-MAPK Ab (Fig. 4C, lower panels). These data suggest that the rapid, transient inactivation of 70k PTP may be important for concomitant PDGFR-mediated phosphorylation and mitogenic signaling.

In attempting to identify the 70k PTP that was oxidized following PDGF stimulation, attention was drawn to the SH2 domain-containing PTP, SHP-2. This PTP has been shown to be associated with tyrosine phosphorylated PDGFR (Lechleider et al., 1993 *J. Biol. Chem.* 268:21478-81). In addition, the apparent molecular weight of SHP-2 on SDS-PAGE is similar to that of the PDGF-responsive 70k PTP detected in Fig. 4. Initially, it was confirmed that SHP-2 could be recruited by the ligand-activated PDGFR in Rat-1 cells. Serum-starved Rat-1 cells were exposed to PDGF (50 ng/ml)

for the indicated times (Fig. 5A). The PDGFR and associated proteins were immunoprecipitated with antibody Ab-X, and pTyr proteins visualized by immunoblotting with anti-pTyr Ab G104 (Fig. 5A, upper panel). The same filter was re-probed with anti-PDGFR, anti-SHP-2, anti-GAP and anti-p85 PI3K Abs. The positions of PDGFR (Fig. 5A, solid arrow) and SHP-2 (Fig. 5A, open arrow) are indicated. As shown in Fig. 5A (upper panel), a tyrosine phosphorylated protein of ~70 kDa by SDS-PAGE associated rapidly with the PDGFR in response to ligand activation. Furthermore, immunoblotting was used to show that SHP-2 comigrated with this 70k phosphoprotein (Fig. 5A, lower panels). The complex between PDGFR and SHP-2 persisted for up to 20 minutes after stimulation, then the level of association decreased (Fig. 5A, lower panels).

To test whether SHP-2 was the 70k PTP that was oxidized following PDGF stimulation, SHP-2 protein was immunodepleted from cell lysates with increasing amounts of anti-SHP-2 antibody, and the supernatants were subjected to the modified in-gel PTP assay. Rat-1 cells, either untreated (-) or stimulated with 50 ng/ml PDGF (+), were harvested in lysis buffer containing 10 mM IAA. Lysates were incubated with antibody to either SHP-2 or SHP-1 and subjected to an in-gel PTP assay (Fig. 5B, upper panel). The arrow denotes the position of the 70k PTP that was inactivated in response to PDGF and immunodepleted from cell lysates with antibodies to SHP-2. The lower panel of Fig. 5B illustrates an immunoblot to show the immunodepletion of SHP-2. As shown in Fig. 5B, anti-SHP-2 antibody depleted the 70k PTP from Rat-1 cell lysates, whereas an anti-SHP-1 antibody control did not. These data identify SHP-2 as a PTP that was rapidly oxidized and inactivated following PDGF stimulation.

Association of other SH2 domain-containing proteins with activated PDGFR was also examined. It has been shown that SHP-2 dephosphorylates the PDGFR on the autophosphorylation sites that function as binding sites for GTPase-activating protein (GAP) and phosphatidylinositol 3 kinase (PI3K) (Klinghoffer and Kazlauskas, 1995 *J. Biol. Chem.* 270:22208-17) (see also Kazlauskas et al., 1992 *Mol. Cell Biol.* 12:2534-44). However, both GAP and the p85 subunit of PI3K were recruited by PDGFR rapidly after ligand stimulation, even though SHP-2 was

associated with the receptor at this time (Fig. 5A). These results suggest that oxidation and inactivation of SHP-2 in response to PDGF may be important for permitting recruitment of GAP and PI3K by the activated PDGFR. Interestingly, GAP and PI3K dissociated from the receptor by 10 minutes after PDGF stimulation (Fig. 5A),  
5 coincident with dephosphorylation of PDGFR $\beta$  (Fig. 5A) and reactivation of SHP-2 (Fig. 4A).

#### EXAMPLE 4

##### 10 SPECIFICITY OF ROS PRODUCTION AND SHP-2 OXIDATION AND INACTIVATION IN RESPONSE TO GROWTH FACTOR STIMULATION

SHP-2 was one of the first PTPs to be recognized as capable of both negative signaling (by antagonizing PTK function) and positive signaling following a  
15 PTP-mediated dephosphorylation event, playing such a role, for example, in the context of EGF and FGF receptor signaling (Bennett et al., 1996 *Mol. Biol. Cell* 16:1189-1202; Saxton et al., 1997 *EMBO J.* 16:2352-64). The data described above, showing oxidation and inhibition of SHP-2 in response to PDGF, appear to be indicative of a negative role in signaling. This example describes additional characterization of a PTP  
20 response to a stimulus that induces a biological signaling pathway.

Treatment of Rat-1 cells with PDGF triggered production of intracellular ROS (Fig. 6A), concomitant with oxidation and inactivation of SHP-2 (Fig. 6B). In contrast, ROS production was not detected in response to either EGF or FGF (Fig. 6A). Rat-1 cells were incubated with 20  $\mu$ M CM-H<sub>2</sub>DCFDA in the dark for 20 mins, then  
25 exposed to peptide growth factors (50 ng/ml) for an additional 10 mins. Images of ROS-induced DCF fluorescence are shown at 50X magnification. (Fig. 6A) The data are representative of 4 independent experiments. In Fig. 6B, Rat-1 cells were exposed to peptide growth factors for the indicated times, lysed in the presence of 10 mM IAA, and oxidized PTPs were visualized by the in-gel PTP assay. In this assay, too,  
30 oxidation and inhibition of SHP-2 was observed following PDGF stimulation of the cells but not following exposure of these cells to EGF or FGF. EGF, FGF and PDGF

all activated MAPK to a similar extent in Rat-1 cells (Fig. 6C). Aliquots of cell lysate from each treatment group were immunoblotted with anti-phospho-MAPK Ab and re-probed with anti-MAPK Ab. These results indicate that, of the stimuli examined in Rat-1 cells, transient oxidation and inactivation of SHP-2 is a specific response to PDGF, consistent with differences in the function of SHP-2 in these distinct growth factor signaling pathways.

The next set of experiments demonstrated that the PDGFR-associated pool of SHP-2 was susceptible to oxidation and inactivation. Recent studies have suggested that a Rac1-associated, plasma membrane-bound NADPH oxidase is responsible for PDGF-induced generation of ROS in non-phagocytic cells (Bae et al., 2000). In light of the short half-life of such ROS, it is possible that their influence on PTPs may be spatially restricted to the subcellular regions proximal to their production.

In preliminary studies only ~10% of the total population of SHP-2 was recruited into a complex with the PDGFR following ligand stimulation in Rat-1 cells. To examine whether this recruitment was required for oxidation and inactivation of SHP-2 in response to PDGF, mutant forms of the PDGFR were constructed that were deficient in their association with SHP-2. Chimeric cell surface signal transduction receptors were also constructed which consisted of the extracellular segment of human granulocyte colony stimulating factor (G-CSF) receptor and the transmembrane and cytoplasmic segments of human PDGFR. The ability of these mutant PDGFRs to induce oxidation of the PTP in response to ligand was then tested.

Full length cDNA encoding wild type (WT) and Y1009F mutant forms of human PDGFR $\beta$  was provided by Dr. Jonathan Cooper (Fred Hutchinson Cancer Center, Seattle, WA; (Kashishian and Cooper, 1993 *Mol. Biol. Cell* 4:49-57)). The cDNA encoding the extracellular segment of human G-CSFR was a gift from Dr. Shigekazu Nagata (Osaka University, Japan; (Fukada et al., 1996)). Chimeric receptors comprising the extracellular segment of G-CSFR fused to the transmembrane and intracellular (WT and Y1009F) segments of PDGFR $\beta$  were constructed in the pcDNA3.1A vector (Invitrogen) by standard PCR protocols then inserted into a pRK5 expression vector for transient transfection experiments. The integrity of the constructs was confirmed by sequencing. These chimeric receptors permitted examination of G-

CSF-induced recruitment of SHP-2 to the chimeric receptors and signaling in Rat-1 cells, which do not express endogenous G-CSF receptor (G-CSFR), while avoiding activation of endogenous PDGFR. The autophosphorylation site at Y 1009 of human PDGFR has been shown to be the major docking site for the N-terminal SH2 domain of SHP-2 (Lechleider et al., 1993).

Expression constructs encoding chimeric receptors comprising either wild type (WT) or Y1009F forms of the PDGFR intracellular segment were transiently transfected into Rat-1 cells. Upon stimulation with G-CSF, both WT and Y1009F chimeric receptors were tyrosine phosphorylated (Fig. 7A). Although both receptors were activated following treatment with G-CSF, only the WT recruited SHP-2, which was recovered in immune-complexes precipitated with antibodies to the intracellular segment of the PDGFR (Fig. 7A). Using the modified in-gel PTP assay, WT chimeric receptors triggered rapid oxidation and inactivation of SHP-2 in response to G-CSF stimulation. Rat-1 cells were transiently transfected with plasmids expressing WT or Y1009F mutant G-CSFR/PDGFR chimeric receptor, or with a plasmid encoding Green Fluorescence Protein (GFP) as a control for expression. After exposure to 100 ng/ml G-CSF for 5 min, the chimeric receptors were immunoprecipitated from lysates with antibody Ab-X and immunoblotted with anti-pTyr Ab G104. (Fig. 7A) Immunoprecipitation of the receptors was verified by immunoblotting with Ab-X. The same filter was stripped and reprobed with anti-SHP-2 Ab. Expression of the chimeric receptors was verified by immunoblotting an aliquot of each lysate with Ab-X, which recognizes the intracellular segment of the PDGFR, and subsequently with anti-G-CSFR Ab, which recognizes the extracellular segment of chimeric receptors, as also shown in Fig. 7A.

Next, transfected Rat-1 cells were treated with G-CSF for the indicated times, lysed in the presence of 10 mM IAA and the lysates subjected to an in-gel PTP assay. (Fig. 7B) Activation of Y1009F mutant receptors did not induce oxidation of SHP-2 (Fig. 7B), suggesting according to non-limiting theory that recruitment of SHP-2 by activated, chimeric PDGFR was required for oxidation of the PTP by ROS generated in response to ligand. The arrow denotes the position of SHP-2.



Using the G-CSF:PDGF receptor chimeras, a time course of exposure to G-CSF illustrated that both WT and Y1009F, SHP-2 docking site mutant receptors were rapidly tyrosine phosphorylated following ligand stimulation. However, whereas tyrosine phosphorylation of the WT receptor was transient, the mutant receptor was maintained at a higher level of phosphorylation throughout the time course (Fig. 7C). The differences were particularly striking at the later time points, following 20 and 30 minutes of ligand stimulation. As shown in Fig. 7C, the WT and mutant chimeric receptors were immunoprecipitated at the indicated times and immunoblotted with anti-pTyr Ab (G104). The same filter was re-probed with anti-PDGFR Ab-X.

The phosphorylation status of MAPKs in the cell lysates was also investigated by immunoblotting analysis with antibodies specific for the phosphorylated and dephosphorylated forms of MAPK. Maximal phosphorylation of p42 and p44 ERKs following 20 minutes of stimulation (Fig. 7D). Fig. 7D shows the results obtained when aliquots of lysate from each treatment group were also subjected to immunoblotting with anti-phospho-MAPK Ab, and then re-probed with anti-MAPK Ab. However, both the extent and duration of ERK phosphorylation was higher in cells expressing the mutant receptor, which was deficient in binding of SHP-2, compared to those expressing the wild type receptor (Fig. 7D & E). As shown in Fig. 7E, densitometric analysis of the gel image of Fig. 7D illustrates the ratio of phosphorylated (upper panel of 7D) over total (lower panel of 7D) MAPK. Without wishing to be bound by theory, these results suggest that recruitment of SHP-2 into the PDGF receptor-containing signaling complex is important for down-regulation of both receptor tyrosine phosphorylation and activation of MAPK, and that oxidation and inhibition of SHP-2 in the early phase of the response to PDGF is important for establishment of the signaling response.

#### EXAMPLE 5

##### PRIOR TREATMENT OF CELLS WITH A PTP ACTIVE SITE-BINDING AGENT PROTECTS AGAINST IAA-MEDIATED PTP INACTIVATION

An in-gel protection assay was developed to show that a small molecule PTP inhibitor could bind to the active site of the PTP and protect the active site cysteine

from alkylation or from other irreversible modifications. An independently developed PTP inhibitor was shown to inhibit PTP catalytic activity and characterized by X-ray crystallography as a PTP active site-binding agent. This PTP inhibitor, referred to here as ASBA-1, was used to demonstrate that the PTP inhibitor could specifically bind to a PTP in an activated blood cell.

Peripheral blood mononuclear lymphocytes were purified from human blood. In 5 ml media (RPMI),  $2 \times 10^7$  cells were incubated in 50  $\mu$ M ASBA-1 (PTP specific inhibitor) for 90 minutes and stimulated with phytohemagglutinin (PHA, 0.5  $\mu$ l of 5.0 mg/ml stock) for 2, 10 or 30 min. Cells were pelleted, washed and lysed in buffer in the presence or absence of 50 mM iodoacetic acid (IAA) in extraction buffer (50mM Tris, pH 7.5; 1mM EDTA; 1mM EGTA; 0.25% Triton X-100; 1ug/mL pepstatin, aprotinin, and leupeptin; 1mM benzamidine). Desalted proteins were separated on a 2ml Source Q anion exchange column (Amersham Pharmacia Biotech) using a 0-1M NaCl gradient in 20mM Tris, pH 7.5; 1mM EDTA; 0.05% Triton X-100. Samples of each fraction were analyzed by the in-gel PTP assay (described above) and the results are shown in Figure 9. At least two IAA-insensitive, PTP activity bands were observed from ASBA-1-treated cells, following autoradiography of the dried gel (Fig. 9, left panel). In samples from cells in which these proteins were not protected by ASBA-1 pretreatment, the PTPs were inactivated by IAA and PTP activity was not observed in the corresponding gel region using the in-gel PTP activity assay (Fig. 9, right panel). Therefore, and according to non-limiting theory, specific binding of ASBA-1 to the active sites of at least two PTPs in these cells prevented complete inactivation of the PTPs by IAA.

25

## EXAMPLE 6

## INSULIN SIGNALING MEDIATED BY ROS PRODUCTION

The role of intracellular production of ROS (*e.g.*, H<sub>2</sub>O<sub>2</sub>) in insulin-mediated signal transduction was examined. Rat-1 fibroblasts were cultured and then serum starved for 16 hours as described in Example 1. The cells were preloaded with 5  $\mu$ M CM-H<sub>2</sub>DCFDA (Molecular Probes, Eugene, OR, Cat. No. D-399) in the dark for

15 min and then exposed to 50 nM insulin for 10 minutes. Images of ROS-induced DCF fluorescence were captured by fluorescence microscopy using a Zeiss Axiovert 405M inverted microscope equipped with a fluorescence attachment and digital camera (see Example 2), and are shown at 50x magnification in Figure 10A.

5                   Ectopic expression of catalase, which suppresses intracellular H<sub>2</sub>O<sub>2</sub> production, impaired both tyrosine phosphorylation of the  $\beta$ -subunit of the insulin receptor (IR-  $\beta$ ) and the phosphorylation of the downstream signaling molecule PKB/Akt in response to insulin stimulation. Rat-1 cells were transiently transfected as described in Example 1 with different quantities of plasmid encoding human catalase (a  
10 gift from Dr. Toren Finkle, NIH, Bethesda MD) or with empty vector. Two days after transfection, cells were serum-deprived, then stimulated with 50 nM insulin (INS) for 10 min. The cells were lysed in 20 mM Hepes (pH 7.5), 1% NP-40, 150 mM NaCl, 10% glycerol, and 200  $\mu$ M Na<sub>3</sub>VO<sub>4</sub> containing 25  $\mu$ g/ml each of aprotinin and  
leupeptin. Immunoblotting and immunoprecipitation were then performed essentially  
15 as described in Example 1. Catalase expression was verified by immunoblotting with an anti-catalase antibody (Calbiochem®, San Diego, CA) as shown in Figure 10B (top panel). The IR- $\beta$  subunit was immunoprecipitated from 400  $\mu$ g of the cell lysate with antibody 29B4 (Santa Cruz). The lysate was separated by SDS-PAGE and then immunoblotted with anti-pYpY<sup>1162/1163</sup> (Biosource International, Camarillo, CA) to  
20 examine the phosphorylation status of the receptor. The immunoblot was subsequently probed with anti-IR- $\beta$  antibody clone C-19 (Santa Cruz) as a loading control (Figure 10B, middle panel). An aliquot of lysate (30  $\mu$ g) was subjected to immunoblotting with anti-phospho-PKB/AKT antibody (Cell Signaling). The same filter was then stripped and re-probed with anti-PKB/AKT antibody (Cell Signaling) as a loading control  
25 (Figure 10B, bottom panel).

## EXAMPLE 7

## INSULIN INDUCES TRANSIENT OXIDATION OF PTP1B AND TC45

The effect of insulin-induced  $H_2O_2$  production on PTP oxidation was  
5 examined using the modified in-gel PTP assay essentially as described in Example 1. Serum-starved Rat-1 cells were exposed to 50 nM insulin for 2, 5, 10, 20, and 30 minutes. Lysates were prepared under anaerobic conditions in the presence of 10 mM IAA and then subjected to in-gel PTP assays. The substrate incorporated into the SDS-PAGE gels for these assays was  $^{32}P$ -labeled reduced, carboxamidomethylated and  
10 maleylated lysozyme (RCML) ( $1.5 \times 10^6$  cpm/20 ml gel solution,  $\sim 2 \mu M$  p-Tyr). Figure 11A shows that a PTP having an approximate molecular weight of 50 kDa and a PTP with an approximate molecular weight of 45 kDa were transiently oxidized in response to insulin.

The oxidized 45 kDa and 50 kDa PTPs were identified as TC-45 and  
15 PTP1B, respectively, by immunodepletion and immunoblotting. Total cell lysates were prepared as described in Example 1. Lysate (400  $\mu g$ ) was incubated with normal IgG, anti-PTP1B antibody (FG6, LaMontagne et al., *Mol. Cell. Biol.* 18:2965-75 (1998)), or anti-TC45 antibody (1910H, Lorenzen et al., *J. Cell. Biol.* 131:631-43 (1995)) coupled to protein G-Sepharose<sup>TM</sup> beads (Amersham Biosciences). After the  
20 immunoprecipitation step, the immune complexes and supernatants were collected and subjected to in-gel PTP assays. Immunodepletion of the 50 kDa PTP from the lysate with anti-PTP1B antibody is shown in Figure 11B, and immunodepletion of the 45 kDa PTP with antibody specific for TC45 is shown in Figure 11C. Cell lysate prior to immunodepletion is represented in the lane marked "Lys" in Figures 11B and 11C.  
25 Total cell lysate and supernatants were separated by SDS-PAGE, transferred to nitrocellulose membranes, and immunoblotted with either anti-PTP1B antibody (Fig. 11B) or anti-TC45 antibody (Fig. 11C). The immunoblots show that each PTP protein is depleted after immunoprecipitation with the specific antibody. The same immunoblots were subsequently reprobed with anti-SHP-2 antibody to illustrate that  
30 comparable amounts of polypeptide were loaded onto each gel.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the  
5 invention. Accordingly, the invention is not limited except as by the appended claims.

## CLAIMS

What is claimed is:

5           1.     A method for identifying a protein tyrosine phosphatase that is reversibly oxidized in a cell, comprising:

              contacting a biological sample comprising a cell that comprises at least one protein tyrosine phosphatase with a stimulus under conditions and for a time sufficient to induce reversible oxidation of at least one protein tyrosine phosphatase in  
10   the cell;

              isolating anaerobically the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and

              determining under reducing conditions a level of dephosphorylation of a  
15   detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and therefrom identifying a protein tyrosine phosphatase that is reversibly oxidized in a cell.

20           2.     The method of claim 1 wherein the protein tyrosine phosphatase is selected from the group consisting of SHP-2, PTP1B, and TC45.

              3.     The method of claim 1 wherein the protein tyrosine phosphatase is selected from the group consisting of PTP1B, PTP-PEST, PTP $\gamma$ , LAR, MKP-1,  
25   CRYPA, PTP $\gamma$ 2, DEP-1, SAP1, PCPTP1, PTPSL, STEP, HePTP, PTPIA2, PTPNP, PTPNE6, PTP $\mu$ , PTPX1, PTPX10, SHP-1, SHP-2, PTPBEM1, PTPBEM2, PTPBYP, PTPesp, PTPoc, PTP-PEZ, PTP-MEG1, MEG2, LC-PTP, TC-PTP, TC45, CD45, LAR, cdc14, RPTP- $\alpha$ , RPTP- $\epsilon$ , RKPTP, LyPTP, PEP, BDP1, PTP20, PTPK1, PTPS31, PTPGMC, GLEPP1, OSTPTP, PTPtep, PTPRL10, PTP2E, PTPD1, PTPD2, PTP36,  
30   PTPBAS, PTPBL, BTPBA14, PTPTyp, HDPTP, PTPTD14, PTP $\alpha$ , PTP $\beta$ , PTP $\delta$ , PTP $\epsilon$ , PTP $\kappa$ , PTP $\lambda$ , PTP $\mu$ , PTP $\rho$ , PTP $\psi$ , PTP $\phi$ , PTP $\zeta$ , PTPNU3 and PTPH1.

4. The method of claim 1 wherein the protein tyrosine phosphatase is a protein tyrosine phosphatase as presented in Figure 8.
5. The method of claim 1 wherein the protein tyrosine phosphatase is a dual specificity phosphatase.
6. The method of claim 1 wherein the protein tyrosine phosphatase substrate comprises phosphorylated poly-(4:1)-Glu-Tyr.
7. The method of claim 6 wherein the phosphorylated poly-(4:1)-Glu-Tyr comprises  $^{32}\text{P}$ .
8. The method of claim 1 wherein the detectably labeled protein tyrosine phosphatase substrate comprises a reporter molecule selected from the group consisting of a fluorophore, a radionuclide, a chemiluminescent agent, an enzyme, an immunologically detectable epitope and a chromophore.
9. The method of claim 8 wherein the fluorophore is selected from the group consisting of fluorescein, rhodamine, Texas Red, AlexaFluor-594, AlexaFluor-488, Oregon Green, BODIPY-FL and Cy-5.
10. The method of claim 1 wherein the protein tyrosine phosphatase substrate comprises a polypeptide sequence derived from a protein selected from the group consisting of PDGF receptor, VCP, p130<sup>cas</sup>, EGF receptor, p210 bcr:abl, MAP kinase, Shc, insulin receptor, lck, T cell receptor zeta chain, and reduced and carboxyamidomethylated and maleylated lysozyme (RCML).
11. The method of claim 1 wherein the sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is an alkylating agent.

12. The method of claim 1 wherein the sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is selected from the group consisting of iodoacetamide, iodoacetic acid, arsenic oxide, maleimide analog, haloacetimido analog, 4-vinylpyrimidine analog and N-ethylmaleimide.

13. The method of claim 1 wherein the cell is a mammalian cell.

10 14. The method of claim 13 wherein the mammalian cell is derived from a cell line.

15 15. The method of claim 14 wherein the cell line is selected from the group consisting of Rat-1 fibroblasts, COS cells, CHO cells and HEK-293 cells.

16. The method of claim 1 wherein the step of isolating the protein tyrosine phosphatase comprises cell lysis.

17. The method of claim 16 wherein the step of isolating further comprises gel electrophoresis of the protein tyrosine phosphatase.

18. The method of claim 17 wherein the step of isolating further comprises electrophoresis of the protein tyrosine phosphatase in a gel comprising the detectably labeled protein tyrosine phosphatase substrate.

19. The method of claim 16 wherein the step of isolating further comprises detecting the protein tyrosine phosphatase with an antibody that specifically binds to the phosphatase.

20. The method of claim 1 wherein the stimulus increases reactive oxygen species in the sample.



21. The method of claim 1 wherein the stimulus is selected from the group consisting of a cytokine, a growth factor, a hormone, a cell stressor and a peptide.

5 22. The method of claim 21 wherein the cell stressor is selected from the group consisting of a source of ROS and ultraviolet light.

23. The method of claim 1 wherein the stimulus is selected from the group consisting of PDGF, EGF, bFGF, insulin, GM-CSF, TGF- $\beta$ 1, IL-1, IL-3, IFN- $\gamma$ ,  
10 TNF- $\alpha$ , PHA, AT-2, thrombin, thyrotropin, parathyroid hormone, LPA, sphingosine-1-phosphate, serotonin, endothelin, acetylcholine, platelet activating factor, bradykinin and G-CSF.

24. A method for identifying a protein tyrosine phosphatase that is  
15 reversibly modified by a PTP active site-binding agent in a cell, comprising:

contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine with a biological sample comprising a cell that comprises at least one protein tyrosine phosphatase;

20 isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and

determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group of a protein tyrosine phosphatase active site  
25 invariant cysteine, a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and therefrom identifying a protein tyrosine phosphatase that is reversibly modified by a PTP active site-binding agent in a cell.

30

25. The method of claim 24 wherein the step of isolating is performed anaerobically.

26. The method of claim 24 wherein the PTP active site-binding agent is selected from the group consisting of an agent that covalently binds to the PTP active site and an agent that non-covalently binds to the PTP active site.

27. The method of claim 24 wherein the PTP active site-binding agent is selected from the group consisting of a sulfonated compound and a vanadate compound.

28. The method of claim 24 wherein the PTP active site-binding agent covalently and reversibly modifies a sulfhydryl group of a PTP active site invariant cysteine.

29. The method of claim 28 wherein the step of determining comprises reversing a covalent modification of a sulfhydryl group of a PTP active site invariant cysteine.

30. The method of claim 29 wherein the step of reversing comprises contacting the PTP with a reducing agent.

31. The method of claim 30 wherein the reducing agent is selected from the group consisting of dithiothreitol, dithioerythritol, and 2-mercaptoethanol.

32. The method of claim 24 wherein the sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is selected from the group consisting of iodoacetamide, iodoacetic acid, arsenic oxide, maleimide analog, haloacetimido analog, 4-vinylpyrimidine analog, and N-ethylmaleimide.

33. A method for identifying a protein tyrosine phosphatase that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising:

contacting a biological sample comprising a cell that comprises at least one protein tyrosine phosphatase with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and thereby reversibly protect a protein tyrosine phosphatase active site invariant cysteine from modification;

isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and

determining, under conditions that reverse the reversible protection of the protein tyrosine phosphatase active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and therefrom identifying a protein tyrosine phosphatase that is a reversibly modified component of an inducible biological signaling pathway in a cell.

34. The method of claim 33 wherein the step of isolating is performed anaerobically.

35. The method of claim 33 wherein the sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine is selected from the group consisting of iodoacetamide, iodoacetic acid, arsenic oxide, maleimide analog, haloacetimido analog, 4-vinylpyrimidine analog, and N-ethylmaleimide.

36. A method for identifying an agent that alters an inducible biological signaling pathway, comprising:

(a) identifying a protein tyrosine phosphatase that is reversibly oxidized in a cell according to a method comprising:

(i) contacting a first biological sample comprising a cell that comprises at least one protein tyrosine phosphatase with a stimulus under conditions and for a time sufficient to induce reversible oxidation of at least one protein tyrosine phosphatase in the cell;

(ii) isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine;

(iii) determining under reducing conditions a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase, wherein detectable substrate dephosphorylation indicates that an active protein tyrosine phosphatase is present, and therefrom identifying a protein tyrosine phosphatase that is reversibly oxidized in a cell;

(b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises the PTP that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of the PTP;

(c) isolating the protein tyrosine phosphatase in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a protein tyrosine phosphatase active site invariant cysteine; and

(d) determining under reducing conditions a level of dephosphorylation of a detectably labeled protein tyrosine phosphatase substrate by the protein tyrosine phosphatase,

wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway,

and wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent

relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

5                   37.    The method of claim 36 wherein the step of isolating in the method recited in (a) is performed anaerobically.

                  38.    The method of claim 36 wherein the step of isolating recited in (c) is performed anaerobically.

10

                  39.    A method for identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is reversibly oxidized in a cell, comprising:

                  contacting a biological sample comprising a cell that comprises SHP-2 with a stimulus under conditions and for a time sufficient to induce reversible oxidation  
15   of SHP-2 in the cell;

                  isolating anaerobically SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and

                  determining under reducing conditions a level of dephosphorylation of a  
20   detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2 comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is reversibly oxidized in a cell.

25

                  40.    A method for identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is reversibly oxidized in a cell, comprising:

                  contacting a biological sample comprising a cell that comprises PTP1B with a stimulus under conditions and for a time sufficient to induce reversible oxidation  
30   of PTP1B in the cell;

isolating anaerobically PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and

determining under reducing conditions a level of dephosphorylation of a  
5 detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, and 12, and wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is reversibly oxidized in a cell.

10

41. A method for identifying a TC45 protein tyrosine phosphatase (TC45) that is reversibly oxidized in a cell, comprising:

contacting a biological sample comprising a cell that comprises TC45 with a stimulus under conditions and for a time sufficient to induce reversible oxidation  
15 of TC45 in the cell;

isolating anaerobically TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine; and

determining under reducing conditions a level of dephosphorylation of a  
20 detectably labeled TC45 substrate by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM\_080422, and wherein detectable substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is reversibly oxidized in a cell.

25

42. A method for identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is reversibly modified by a PTP active site-binding agent in a cell, comprising:

contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine with a biological  
30 sample comprising a cell that comprises SHP-2;

isolating SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and

determining, under conditions that are capable of reversing a reversible  
5 modification of a sulfhydryl group of a SHP-2 active site invariant cysteine, a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2 comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a  
10 SHP-2 that is reversibly modified by a PTP active site-binding agent in a cell.

43. A method for identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is reversibly modified by a PTP active site-binding agent in a cell, comprising:

15 contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine with a biological sample comprising a cell that comprises PTP1B;

isolating PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant  
20 cysteine; and

determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group of a PTP1B active site invariant cysteine, a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of  
25 SEQ ID NOS: 2, 4, 6, 8, 10, and 12, and wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is reversibly modified by a PTP active site-binding agent in a cell.

44. A method for identifying a TC45 protein tyrosine phosphatase  
30 (TC45) that is reversibly modified by a PTP active site-binding agent in a cell, comprising:

contacting a PTP active site-binding agent that is capable of reversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine with a biological sample comprising a cell that comprises TC45;

isolating TC45 in the presence of a sulfhydryl-reactive agent that is  
5 capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine; and

determining, under conditions that are capable of reversing a reversible modification of a sulfhydryl group of a TC45 active site invariant cysteine, a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein TC45  
10 comprises a polypeptide comprising an amino acid sequence set forth in NM\_080422, and wherein detectable substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is reversibly modified by a PTP active site-binding agent in a cell.

15 45. A method for identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising:

contacting a biological sample comprising a cell that comprises SHP-2 with a stimulus that induces a biological signaling pathway under conditions and for a  
20 time sufficient to induce the biological signaling pathway and thereby reversibly protect a SHP-2 active site invariant cysteine from modification;

isolating the SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and

25 determining, under conditions that reverse the reversible protection of the SHP-2 active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2 comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32, and wherein detectable substrate dephosphorylation indicates  
30 that an active SHP-2 is present, and therefrom identifying a SHP-2 that is a reversibly modified component of an inducible biological signaling pathway in a cell.



46. A method for identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising:

5                   contacting a biological sample comprising a cell that comprises PTP1B with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and thereby reversibly protect a PTP1B active site invariant cysteine from modification;

10                   isolating the PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and

                  determining, under conditions that reverse the reversible protection of the PTP1B active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B  
15                   comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, and 12, and wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is a reversibly modified component of an inducible biological signaling pathway in a cell.

20

47. A method for identifying a TC45 protein tyrosine phosphatase (TC45) that is a reversibly modified component of an inducible biological signaling pathway in a cell, comprising:

25                   contacting a biological sample comprising a cell that comprises TC45 with a stimulus that induces a biological signaling pathway under conditions and for a time sufficient to induce the biological signaling pathway and thereby reversibly protect a TC45 active site invariant cysteine from modification;

30                   isolating the TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine; and

determining, under conditions that reverse the reversible protection of the TC45 active site invariant cysteine from modification, a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM\_080422, and wherein  
5 detectable substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is a reversibly modified component of an inducible biological signaling pathway in a cell.

48. A method for identifying an agent that alters an inducible  
10 biological signaling pathway, comprising:
- (a) identifying a SHP-2 protein tyrosine phosphatase (SHP-2) that is reversibly oxidized in a cell according to a method comprising:
    - (i) contacting a first biological sample comprising a cell that comprises SHP-2 with a stimulus under conditions and for a time sufficient to  
15 induce reversible oxidation of SHP-2 in the cell;
    - (ii) isolating SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a SHP-2 active site invariant cysteine;
    - (iii) determining under reducing conditions a level of  
20 dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein detectable substrate dephosphorylation indicates that an active SHP-2 is present, and therefrom identifying a SHP-2 that is reversibly oxidized in a cell;
  - (b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises SHP-2 that is  
25 reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of SHP-2;
  - (c) isolating SHP-2 in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a SHP-2 active site invariant cysteine; and
  - (d) determining under reducing conditions a level of  
30 dephosphorylation of a detectably labeled SHP-2 substrate by SHP-2, wherein SHP-2

comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 14, 16, 26, 28, 30, and 32,

wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway,

wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

49. A method for identifying an agent that alters an inducible biological signaling pathway, comprising:

(a) identifying a PTP1B protein tyrosine phosphatase (PTP1B) that is reversibly oxidized in a cell according to a method comprising:

(i) contacting a first biological sample comprising a cell that comprises PTP1B with a stimulus under conditions and for a time sufficient to induce reversible oxidation of PTP1B in the cell;

(ii) isolating PTP1B in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a PTP1B active site invariant cysteine;

(iii) determining under reducing conditions a level of dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein detectable substrate dephosphorylation indicates that an active PTP1B is present, and therefrom identifying a PTP1B that is reversibly oxidized in a cell;

(b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises PTP1B that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of PTP1B;

(c) isolating PTP1B in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a PTP1B active site invariant cysteine; and

(d) determining under reducing conditions a level of  
5 dephosphorylation of a detectably labeled PTP1B substrate by PTP1B, wherein PTP1B comprises a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, and 12,

wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent  
10 relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway,

and wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent  
15 relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

50. A method for identifying an agent that alters an inducible  
20 biological signaling pathway, comprising:

(a) identifying a TC45 protein tyrosine phosphatase (TC45) that is reversibly oxidized in a cell according to a method comprising:

(i) contacting a first biological sample comprising a cell that comprises TC45 with a stimulus under conditions and for a time sufficient to  
25 induce reversible oxidation of TC45 in the cell;

(ii) isolating TC45 in the presence of a sulfhydryl-reactive agent that is capable of irreversibly modifying a sulfhydryl group of a TC45 active site invariant cysteine;

(iii) determining under reducing conditions a level of  
30 dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein detectable

substrate dephosphorylation indicates that an active TC45 is present, and therefrom identifying a TC45 that is reversibly oxidized in a cell;

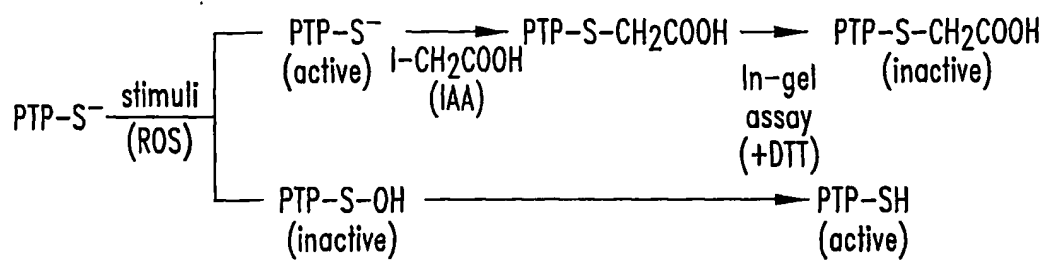
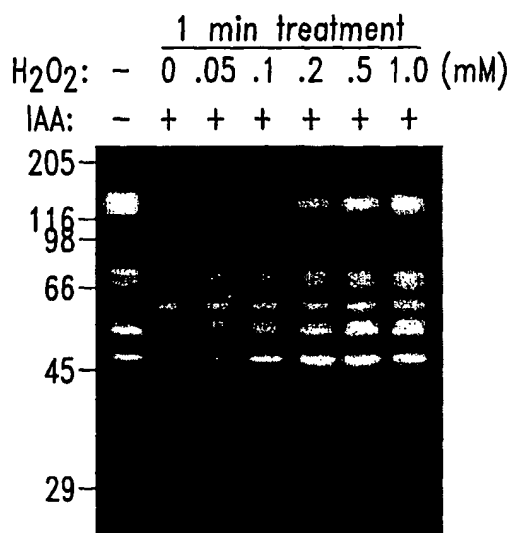
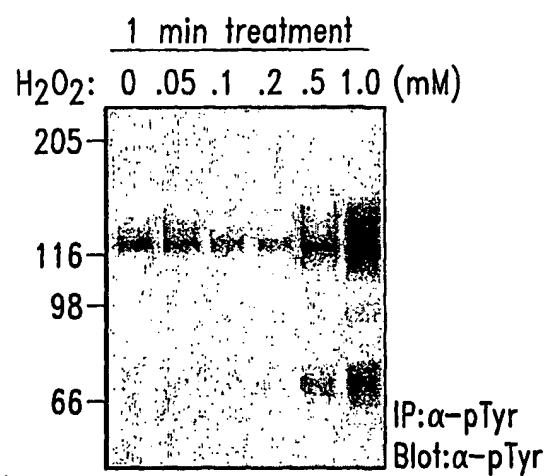
(b) contacting, in the presence and absence of a candidate agent, a second biological sample comprising a cell that comprises TC45 that is reversibly oxidized as identified according to the method of (a) with the stimulus under conditions and for a time sufficient to induce reversible oxidation of TC45;

(c) isolating TC45 in the presence of a sulfhydryl-reactive agent that is capable of covalently modifying a sulfhydryl group of a TC45 active site invariant cysteine; and

(d) determining under reducing conditions a level of dephosphorylation of a detectably labeled TC45 substrate by TC45, wherein TC45 comprises a polypeptide comprising an amino acid sequence set forth in NM\_080422,

wherein a level of substrate dephosphorylation that is decreased when the second sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is an inhibitor of an inducible biological signaling pathway,

and wherein a level of substrate dephosphorylation that is increased when the sample is contacted with the stimulus in the presence of the candidate agent relative to the level of substrate dephosphorylation when the sample is contacted with the stimulus in the absence of the agent indicates that the agent is a potentiator of an inducible biological signaling pathway.

*FIG. 1**FIG. 2A**FIG. 2B*

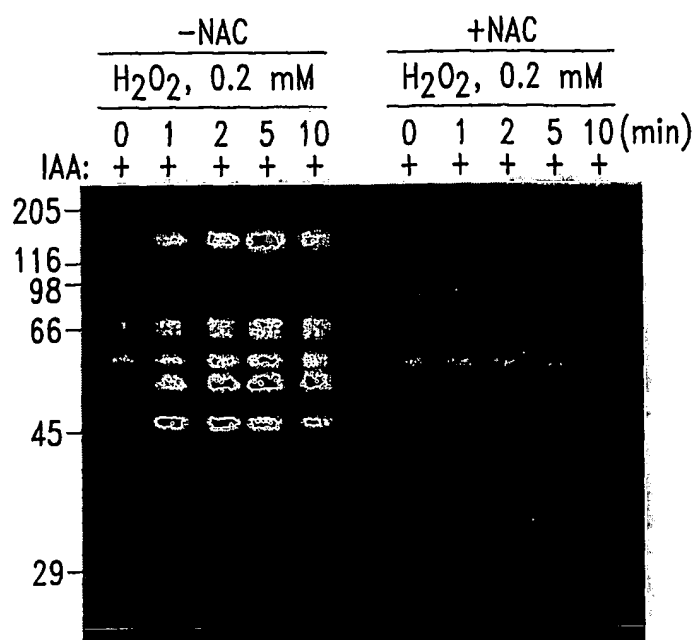


FIG. 2C

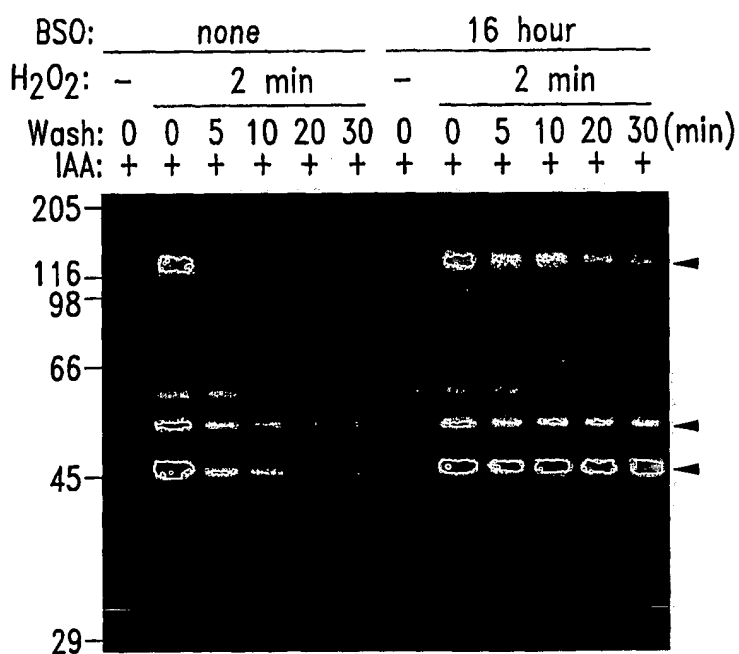
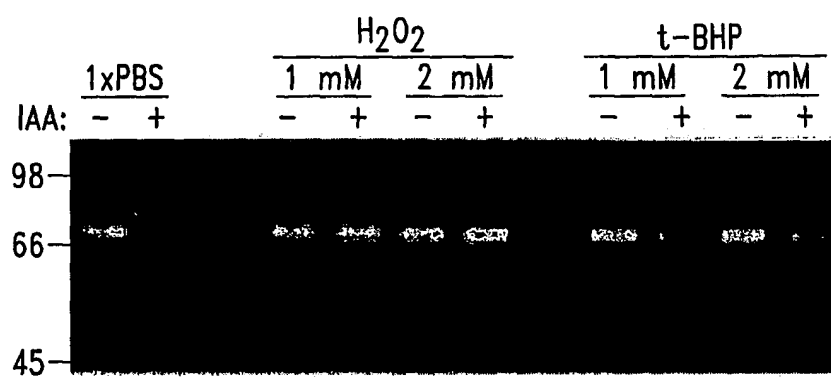


FIG. 2D

*FIG. 3A*



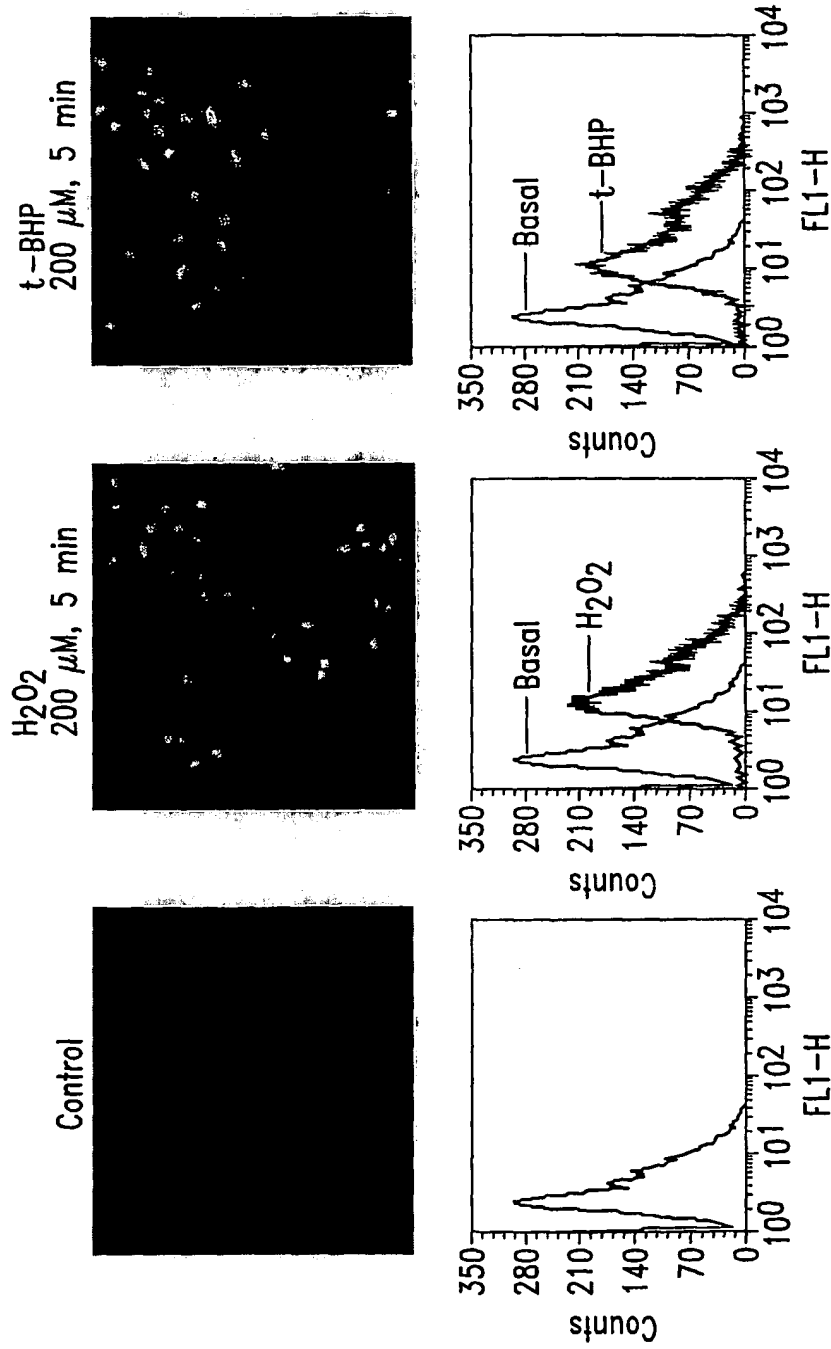
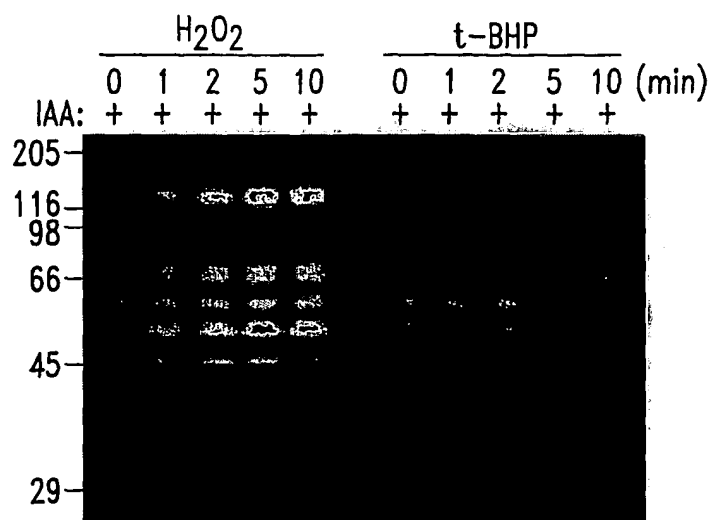
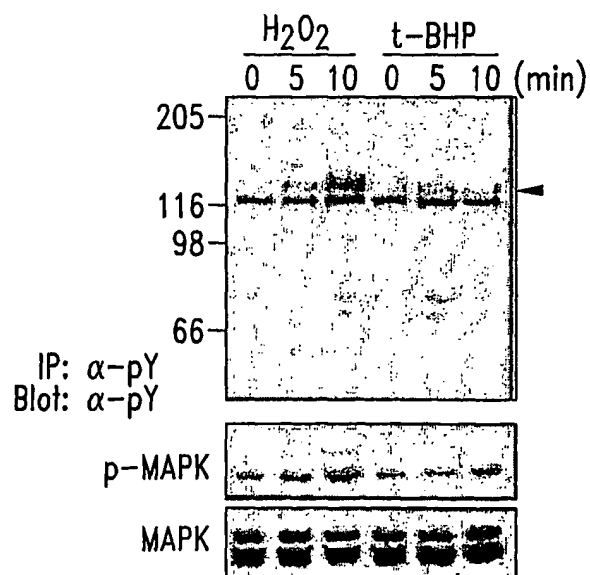


FIG. 3B

*FIG. 3C**FIG. 3D*

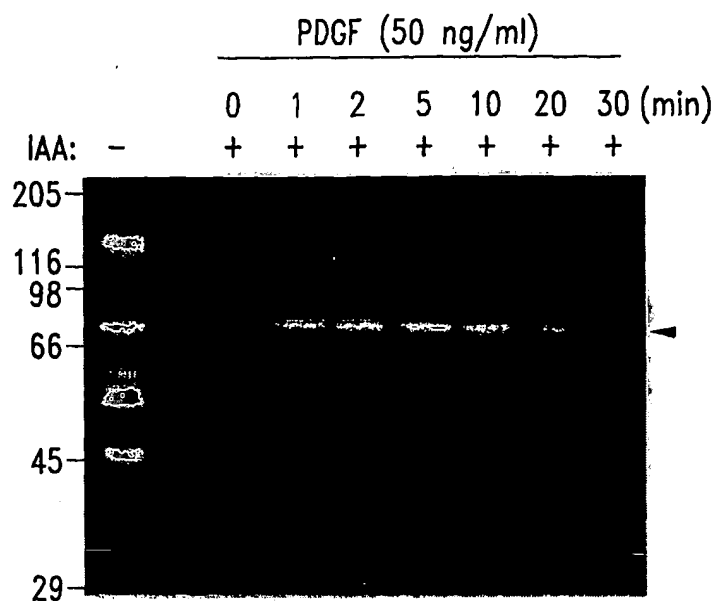


FIG. 4A

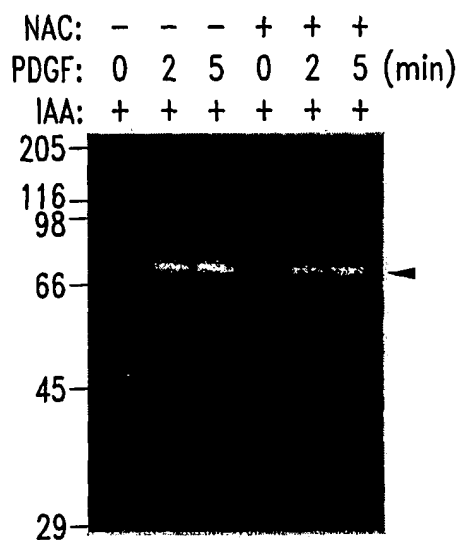


FIG. 4B

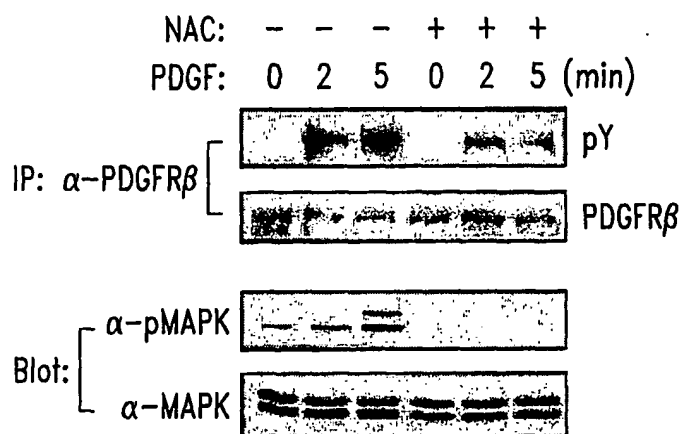


FIG. 4C

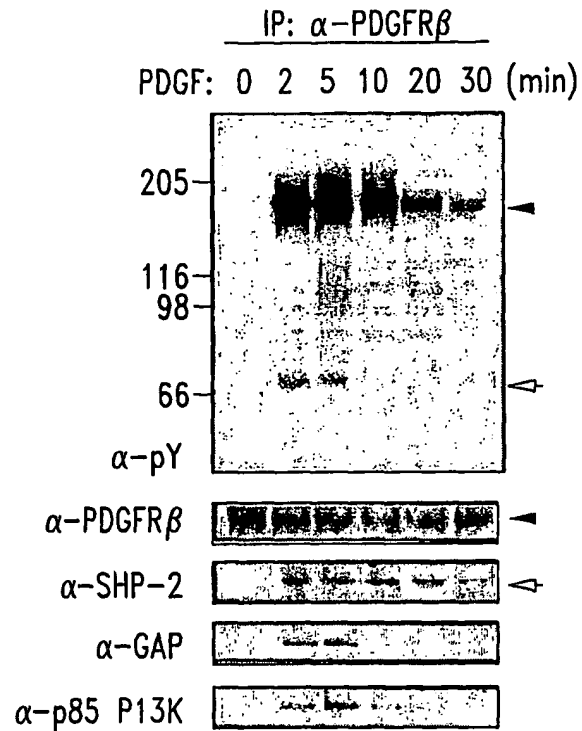


FIG. 5A

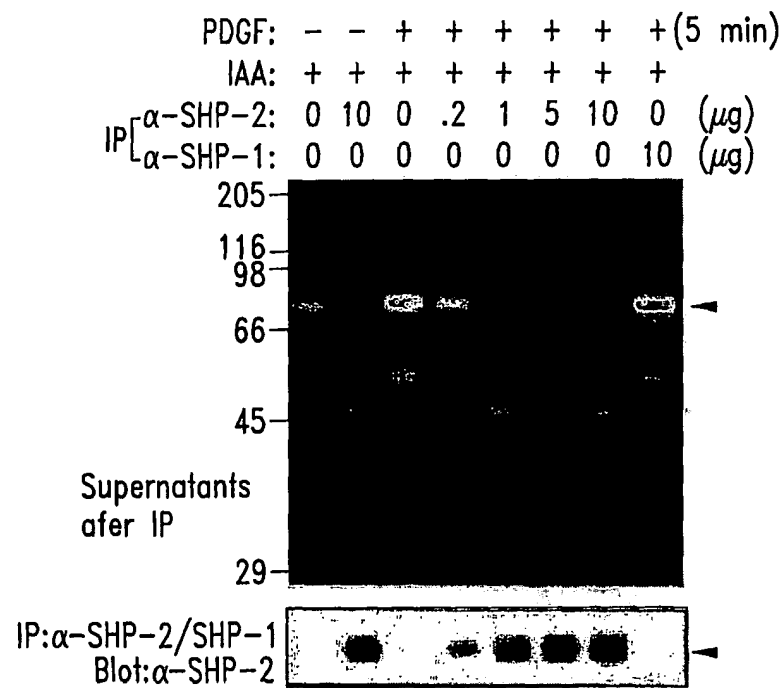
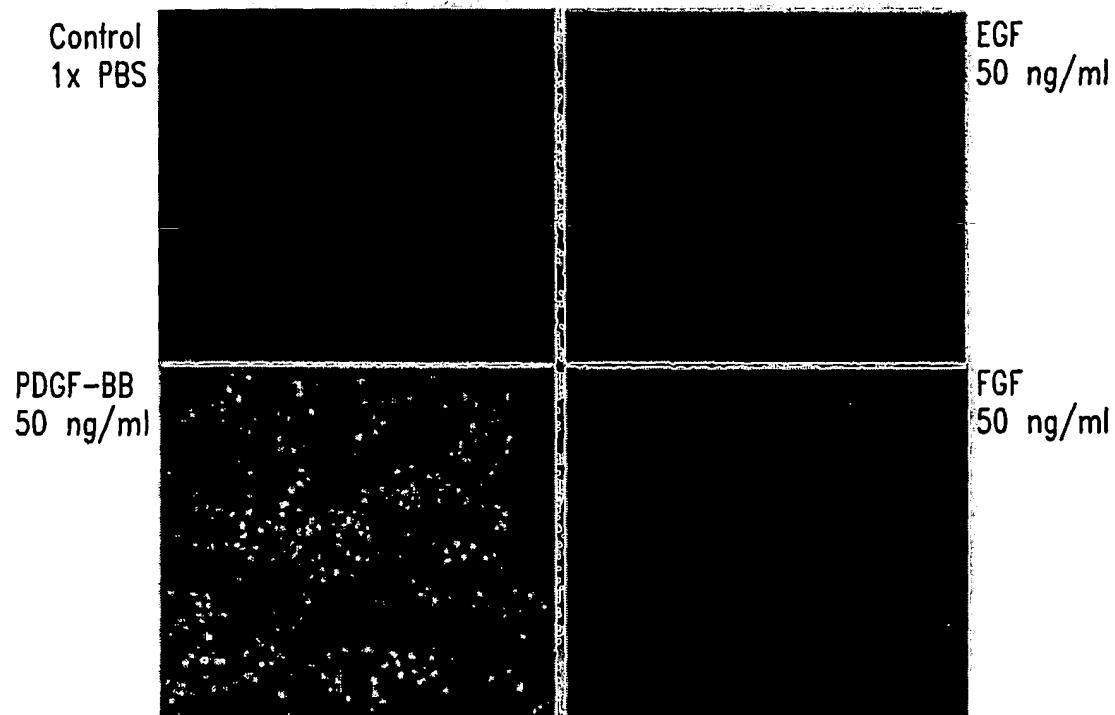


FIG. 5B

*FIG. 6A*

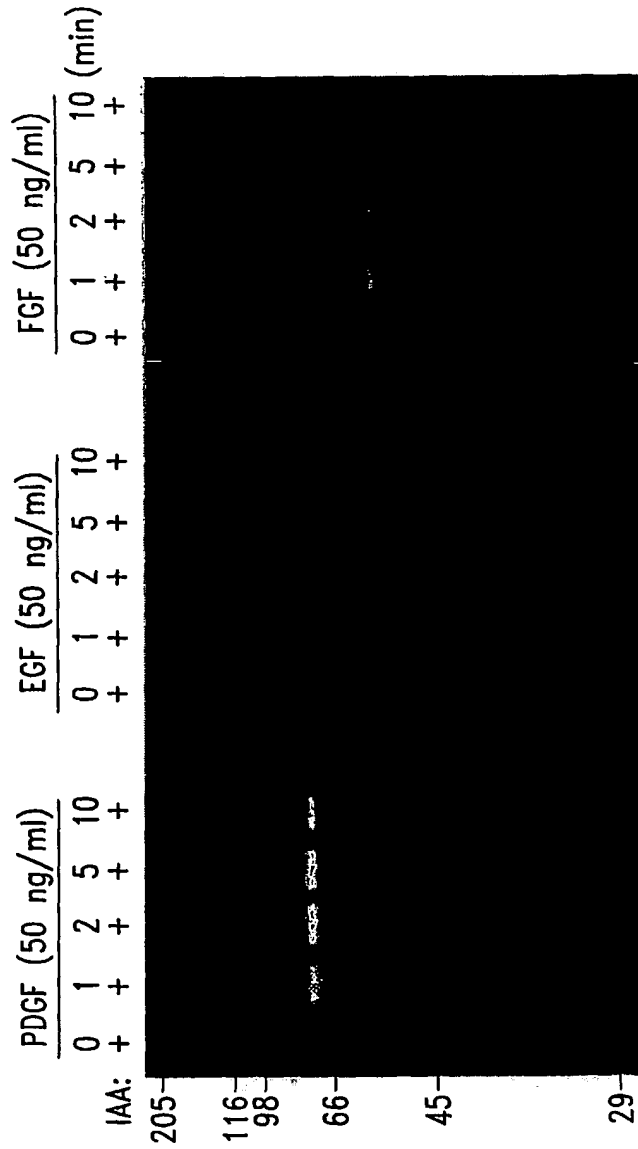


FIG. 6B

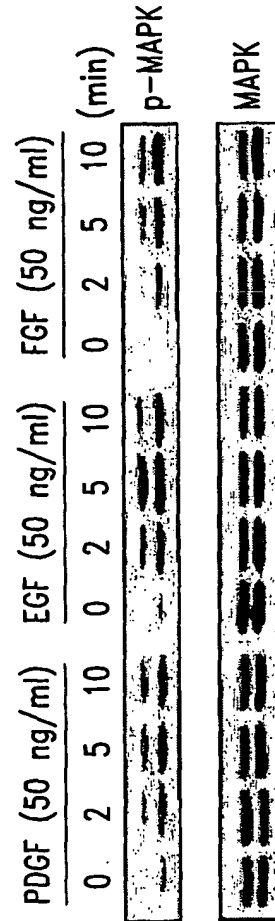


FIG. 6C

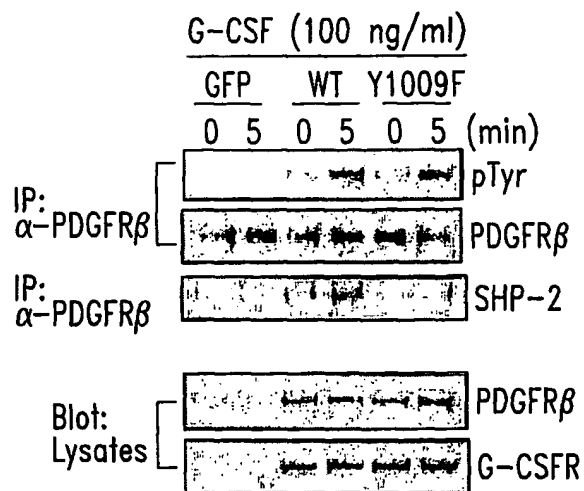


FIG. 7A

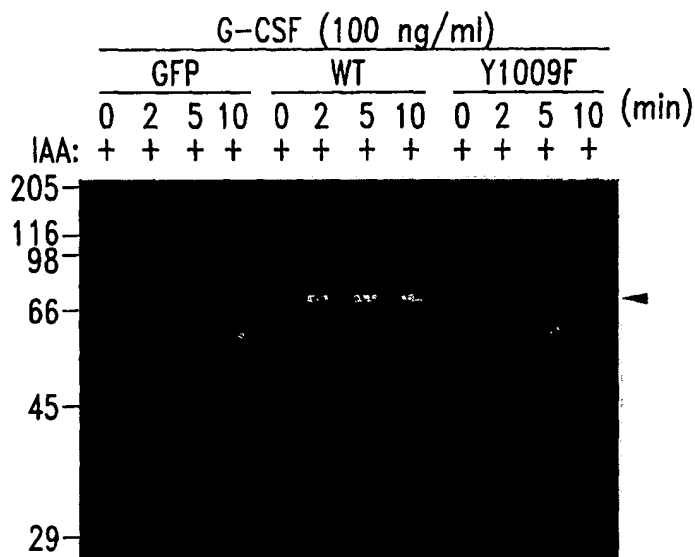


FIG. 7B

G-CSF (100 ng/ml)/IP: $\alpha$ -PDGFR $\beta$ 

WT						Y1009F					
0	2	5	10	20	30	0	2	5	10	20	30

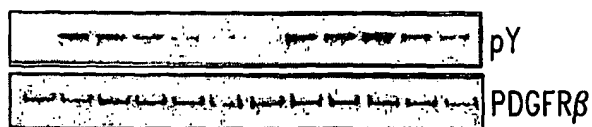


FIG. 7C

G-CSF (100 ng/ml)

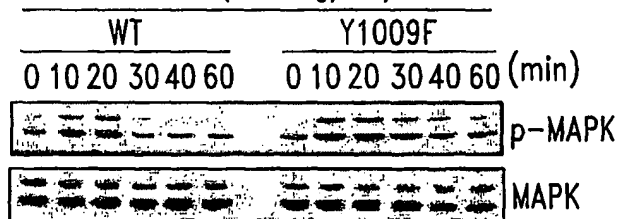


FIG. 7D

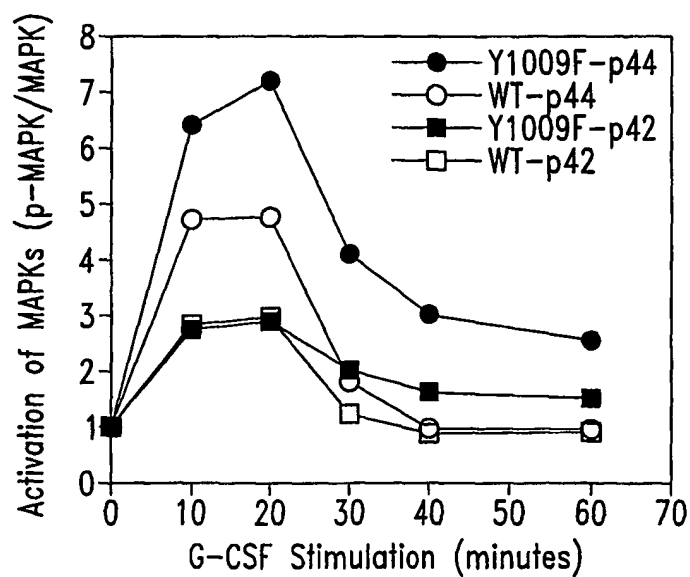


FIG. 7E



Compilation of nonredundant set of 113 vertebrate PTPs

Name	Subtype	Human ortholog	Full-length name	Synonym(s)	Swiss-Prot	GenBank accession no.
<b>Non-RPTP subtypes</b>						
hPTP1B	NT1		PTP1B	PTP-1, PTP-1B	P18031	M31724, M33589,
mPTP1B	NT1	PTP1B	PTP1B	PTP-1, H42, PTP-H42	P35821	U24700, Z23057, M97590, L40595
rPTP1B	NT1	PTP1B	PTP1B	PTP-1	P20417	M33962
cPTP1B	NT1	PTP1B	PTP1B		O13016	U06410
zPTP1B	NT1	PTP1B	PTP1B			AF097481, AF097482, AF097483
hTCPTP	NT1		TC-PTP (T-cell phosphatase)	PTP-2	P17706	M25393, M91478, M90737
mTCPTP	NT1	TCPTP	TC-PTP (T-cell phosphatase)	PTP-2	O06180	S52655, M31477, M30739
rTCPTP	NT1	TCPTP	TC-PTP (T-cell phosphatase)	PTP-2, PTP-S	P35233	Y58828
hSHIP1	NT2		Src homology domain 2-containing PTP1	SH-PTP1, SHP, HCP, PTP1C	P29350	M74903, X62055, M77273, M90388, X82817, X82818
mSHIP1	NT2	SHIP1	Src homology domain 2-containing PTP1		P29351	M68902, M90389, U65953, U65954, U65955
rSHIP1	NT2	SHIP1	Src homology domain 2-containing PTP1			U77038
hSHIP2	NT2		Src homology domain 2-containing PTP2	SH-PTP2, SH-PTP3, Syp, PTP-2C, PTP1D	O06124	D13540, L03535, L07527, X70766, L08807, S78088, S398383
mSHIP2	NT2	SHIP2	Src homology domain 2-containing PTP2	SH-PTP2, Syp	P35235	L08663, D84372
rSHIP2	NT2	SHIP2	Src homology domain 2-containing PTP2	PTP-1D	P41499	U09307, J05963, D83016
cSHIP2	NT2	SHIP2	Src homology domain 2-containing PTP2	SH-PTP2, Syp		U38620
xSHIP2	NT2	SHIP2	Src homology domain 2-containing PTP2			U15287
hMEG2	NT3		Megakaryocyte-PTP2		P43378	M83738
mMEG2	NT3	MEG2	Megakaryocyte-PTP2			AF013490
xPTPX1	NT3	--				L33098
xPTPX10	NT3	--				L33099
hPEST	NT4		Pro, Glu, Ser, Thr-rich PTP	PTP-PEST, PTP61	O05209	D13380, M93425, S69184
mPEST	NT4	PEST	Pro, Glu, Ser, Thr-rich PTP	PTPP19	P35831	M85781, X63440, S36169
rRPTP	NT4	PEST	Rat kidney PTP			D38072
hLYPTP	NT4		Lymphoid phosphatase	Lyp1, Lyp2		AF001846, AF001847, AF077031, AF150732

FIG. 8A

Name	Subtype	Human ortholog	Full-length name	Synonym(s)	Swiss-Prot	GenBank accession no.
mPEP	NT4	LyTP	Hematopoietic cell PTP		P29352	M90388
hBDP1	NT4		Brain-derived phosphatase 1			X79568
rPTP20	NT4	BDP1				U69673
mPTPK1	NT4	BDP1		PTPFLP1 (fetal liver phosphatase 1)		U35124, U52523, U49853
hMEG1	NT5		Megakaryocyte-PTP1	PTPGL, PTPF36-15	P29074	M68941, A4826477
mPTPcep	NT5	MEG1	Testis-enriched phosphatase	PTPMEG		AF106702
zPTPK1	NT5			MEG1		AF097477, AF097478, AF097479, AF097480
hPTPK1	NT5	PTPK1			P26045	M64572, S39392
mPTPKL10	NT6					
rPTPZE	NT6	PTPD1			Q62136	D37801, D83072
hPTPD1	NT6	PTPD1			Q62728	U17971, U18283
hPTPD2	NT6	PTPD1			Q16825	X79510
mPTP36	NT6	PTPD2		PEZ (phosphatase ezrin-like)	Q15678	X82676
					Q62130	D31842
hPTPBAS	NT7		FAS-associated PTP1	BAS, PTP1E, PTP1L, FAP-1, PTP1L, CD95	Q12923	X80289, U12128, D21209, D21210, D21211, U01561, X79576
mPTPBL	NT7	PTPBAS		CDZTP, PTPRIP		D28529, Z32740, D83966
hPTPBAL4	NT7	PTPBAS				U20807
hPTPTyp	NT8		Testis-specific tyrosine phosphatase	Typ		AL050040
mPTPTyp	NT8	PTPTyp	Testis-specific tyrosine phosphatase	Typ		D64141

FIG. 8B

Name	Subtype	Human ortholog	Full-length name	Synonym(s)	Swiss-Prot	GenBank accession no.
hPPTP	NT9		His domain-containing PTP	HD-PTP, PTPD14		T14756, AB025194, AB040904, AL110210, AF169350
rPTPD14	NT9	HDPTP				AF077000
RPP subtypes						
hCD45	RL/R6		Cluster of differentiation 45	Leukocyte common antigen (LCA), T200, PTPNC	P08575	Y00638, Y00652
mCD45	RL/R6	CD45	Cluster of differentiation 45	LCA, T200, Ly5	P06800	M14342, M92933, K33482
rCD45	RL/R6	CD45	Cluster of differentiation 45	Leukocyte common antigen	P04157	M10072, Y00065, M25820, M25821, M25822, M25823, K03039
cPTP lambda	RL/R6	CD45	PTP lambda			L13285, Z12960
xCD45	RL/R6	CD45	Cluster of differentiation 45			AF024438
hPTP lambda	R2A		RPTP lambda	PC2, PTPmicron, PTPmi, PTPpi, PTPro	Q92729	U60289, X97198, U73727, U71075, X95712, AL049570
mPTP lambda	R2A	PTPA	RPTP lambda	PTPtp1, PTPpsi		U55057, D88187
rPTPpsi	R2A	PTPI	RPTPpsi			U66566
hPTPkappa	R2A		RPTPkappa		Q15262	L77886, Z70660
mPTPkappa	R2A	PTPκ	RPTPkappa		P35822	L10106
hPTPmu	R2A		RPTPmu		P28827	X58288
mPTPmu	R2A	PTPμ	RPTPmu		P28828	X58287
hPTPrho	R2A		RPTPrho			AF043644, AL024473, AL022239, Z93942
mPTPrho	R2A	PTPr	RPTPrho			AF152556
xPTPrho	R2A	PTPr	RPTPrho			AF173857
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mLAR	R2B	LAR	LCA-related PTP	PTP-LAR		Z37988
rLAR	R2B	LAR	LCA-related PTP	PTP-LAR		L11586, U00477, X83546, X83505
xLAR	R2B	LAR	LCA-related PTP	PTP-LAR		AF197945
hPTPdelta	R2B	PTPδ	RPTPdelta		P23468	X54133, L38929
mPTPdelta	R2B	PTPδ	RPTPdelta			D13903
cLAR	R2B	PTPδ	RPTPdelta	CNPalpha		L32780
xPTPdelta	R2B	PTPδ	RPTPdelta			AF197944
hPTPsigma	R2B		RPTPsigma			U35234, U40317, U41725, AC005788, S78080, S78086

FIG. 8C

Name	Subtype	Human ortholog	Full-length name	Synonym(s)	Swiss-Prot	GenBank accession no.
rPTPsgma	R2B	PTPσ	RPTPsgma	LAR-PTP2, PTP-PS, PTP-P1		L11597, AF073999
mPTPNUG3	R2B	PTPσ		PTPsgma, PTP19a, PTP19b		X82288, D28530, D28531
xCRTPalphia	R2B	PTPσ				AF198450
hPTPS31	R3					I32038, I32036, I32037, I32035, I32039
rPTPENC	R3	PTPS31	Glomerular mesangial cell receptor	PTPRQ, PTPKCL		AF063249
hGLEPPI	R3		Glomerular epithelial protein 1	PTP12, PTProt		U20489, Z48541
mPTPphi	R3	GLEPPI		PTP-BK, PTP-ro, mGLEPPI		U37465, U37466, U37467, AF295638
rPTPBEH1	R3	GLEPPI	Brain-enriched membrane-associated PTP1	PTP030, BSM-1		D45412, U28938
ratPTPoc	R3	GLEPPI	Osteoclastic PTP			U32587
cPTPcrp2	R3	GLEPPI		CRYP-2		U65891
hPTPbeta	R3		RPTPβ		P23467	X54131
mPTPbeta	R3	PTPβ		Vascular endothelial PTP (VE-PTP)		X58289, AF157628
hDEP1	R3		Density-enhanced PTP	PTPeta, CD148, F-36-12	Q12913	U10886, U37781, AA826475
mPTPBYPP	R3	DEP1	RPTPbeta-like PTP	PTPeta	Q64455	D45212
rDEP1	R3	DEP1	Density enhanced PTP	Vascular PTP-1		U40790
hSNP1	R3		Stomach cancer-associated PTP	hPTPH		D15049, AF91411
rPTPBEH2	R3	SNP1	Brain-enriched membrane-associated PTP2			D45413
mPTPesp	R3	--	Embryonic stem cell PTP	OST-PTP	P70289	U65488, AF300701
rOSTPTP	R3	--	Osteotesticular PTP		Q64612	L36884
hRTPalphia	R4		RPTPalphia		P10433	M34668, X54130, X54890, X53364
mRTPalphia	R4	PTPα	RPTPalphia	LCA-related PTP	P18052	M36033, M33671, M36034
rRTPalphia	R4	PTPα	RPTPalphia		Q03348	L01702
cRTPalphia	R4	PTPα	RPTPalphia			Z32749, L22437,
xRTPalphia	R4	PTPα	RPTPalphia			U09135
hRTPepsilon	R4		RPTPepsilon		P23469	X54134
mRTPepsilon	R4	PTPε	RPTPepsilon			U65368, U66758, U63484, U62387, U40280
rRTPepsilon	R4	PTPε	RPTPepsilon		P49446	D78610, D78613

FIG. 8D

Name	Subtype	Human ortholog	Full-length name	Synonym(s)	Swiss-Prot	Genbank accession no.
hPTPgamm	R5		RPTPgamm		P23470	L09247, X54132
mPTPgamm	R5	PTPy	RPTPgamm		Q05909	L09562
cPTPgamm	R5	PTPy	RPTPgamm		Q98936	U38349
cPTPzeta	R5		RPTPzeta			L27625
hPTPzeta	R5	PTPζ	RPTPzeta		P23471	M93426, X54135, U88957
rPTPzeta	R5	PTPζ	RPTPzeta		Q62656	U09357
hPCPTP1	R7		PC12-derived PTP	PTPc1g, PTPCONL, hCh1PTPα, PTPC		D64053, U77916, U77917, U42361, X82635, Z79693
rPCPTP1	R7	PCPTP	PC 12-derived PTP	PC12-PTP1, CRPTP		D38292, D64050, U14914
mPTPSL	R7	PCPTP		PTP807, PTP-SL, PC 12-PTP1		Z30313, AF041866, D31898
hSTEP	R7		Striatum-enriched phosphatase		P54829	U27831
mSTEP61	R7	STEP	Striatum-enriched phosphatase		P54830	U28217, S80329, U28216
rSTEP	R7	STEP	Striatum-enriched phosphatase		P35234	S49400
hHePTP	R7		Hematopoietic PTP	Leucocyte PTP	P35236	M64322, D11327
rLCPTP	R7	HePTP	Leukocyte PTP	Hematopoietic PTP	P49445	U28356
IA2 Receptor-Like subtype						
hPTPIA2	R8		Islet cell antigen	Islet cell antigen, ICA-512	Q16849	L18983, Z48226, X62899
mPTPIA2	R8	IA2	Islet cell antigen	PTP35	Q60673	U11812, X74438
rPTPIA2	R8	IA2	Islet cell antigen	BBH-3, PTPN, ICA105, PTPLP	Q63259	D45414, X92553, D38222, U40652
bPTPIA2	R8	IA2	Islet cell antigen	ICA512	P55722	AF075170
hPTPIA2beta	R8		PTP-IA-2beta	IA2, RPTPX	Q92932	U65065, AF007555, L76258, U81561, AB002385
mPTPIA2	R8	IA2β	Nervous system and pancreatic PTP	IA2beta, RPTPX, PTPNP-2	P80560	U57345
macPTPIA2beta	R8	IA2β		IA2beta	Q02895	U91574
rPTPIA2E6	R8	IA2β		IA2beta, phogrin	Q63475	U73458, Z50735

FIG. 8E

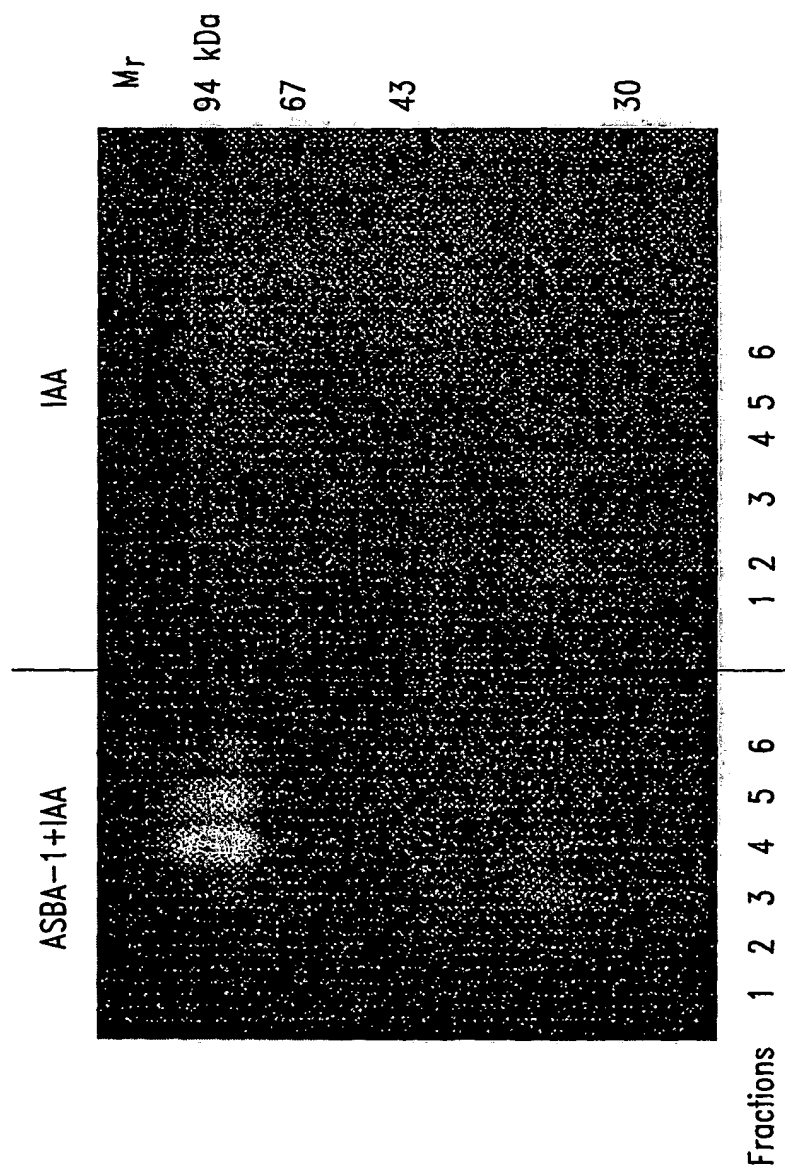


FIG. 9

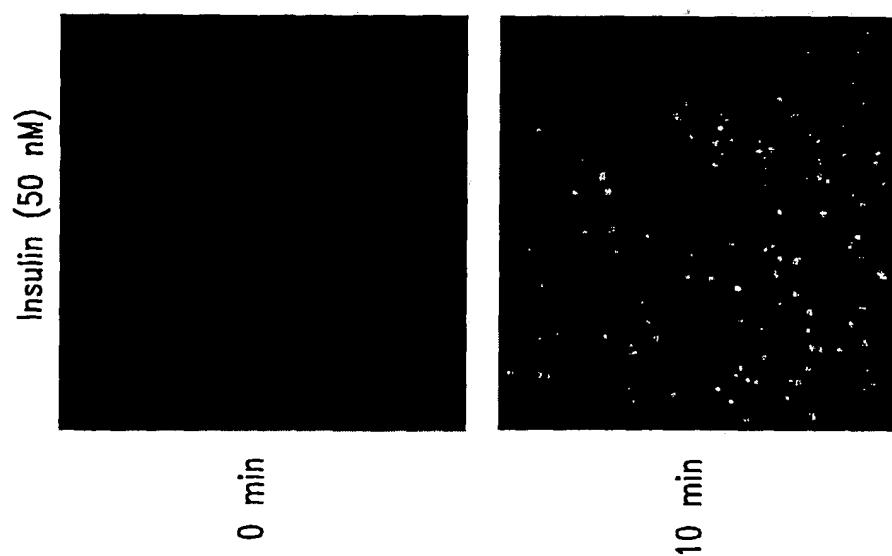


FIG. 10A

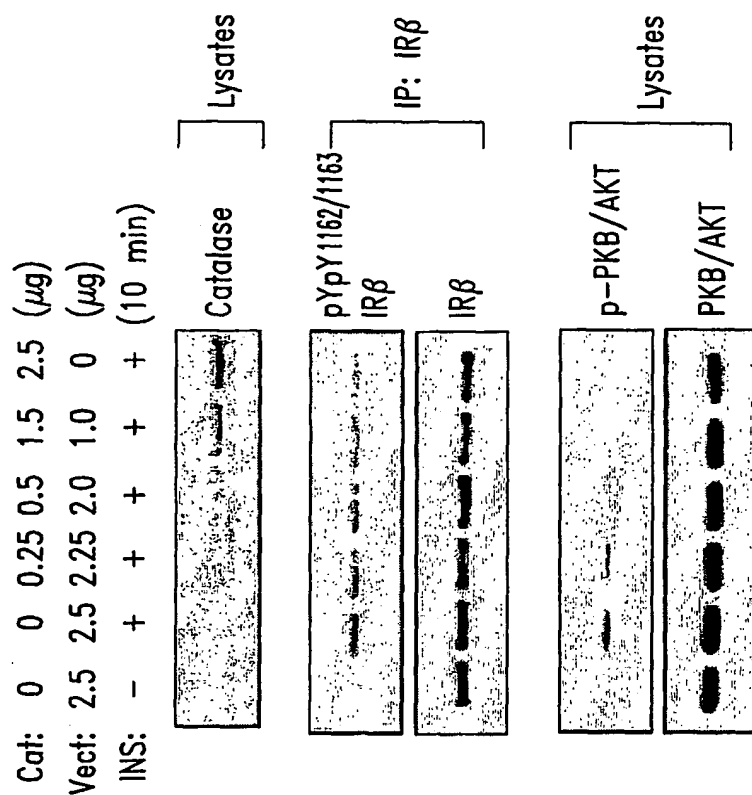
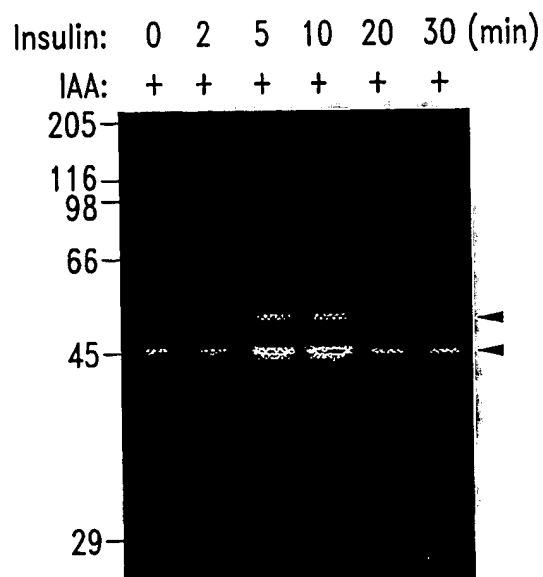
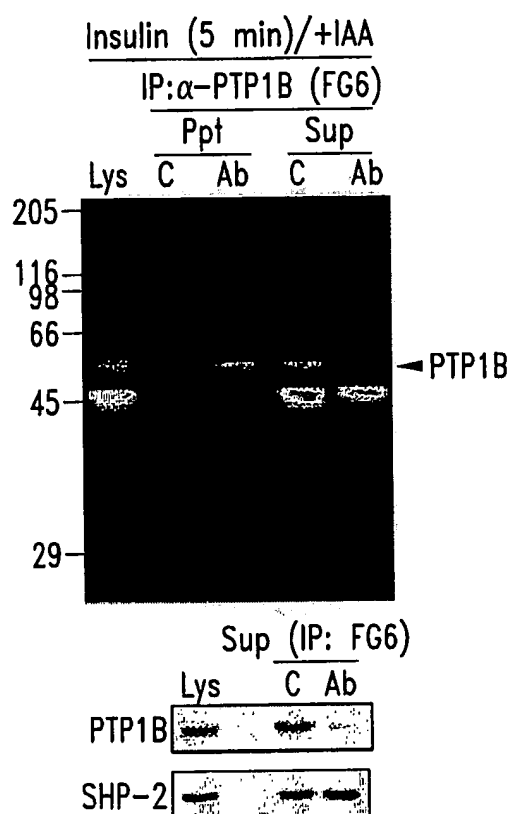
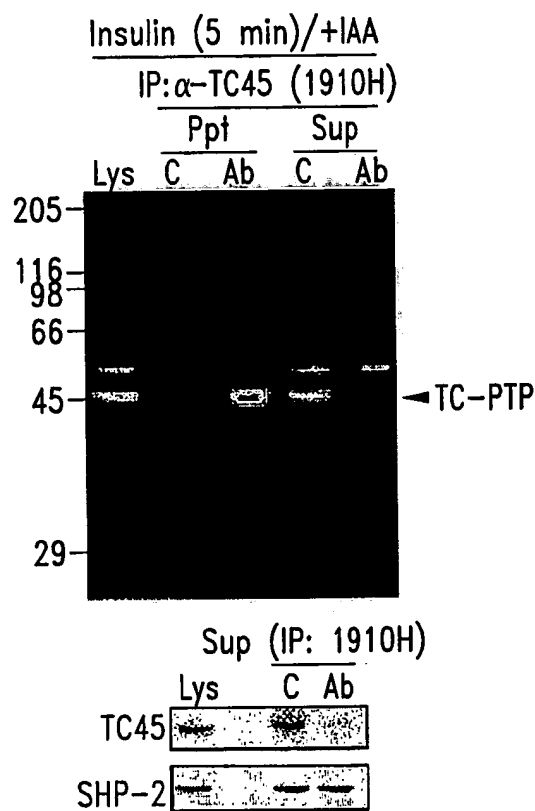


FIG. 10B

*FIG. 11A**FIG. 11B**FIG. 11C*



## SEQUENCE LISTING

<110> Cold Spring Harbor Laboratory  
 Ceptyr, Inc.  
 Tonks, Nicholas K.  
 Meng, Tzu-Ching  
 Cool, Deborah E.

<120> REVERSIBLE OXIDATION OF PROTEIN TYROSINE  
 PHOSPHATASES

<130> 200125.439PC

<140> PCT

<141> 2003-02-13

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&lt;210&gt; 4

&lt;211&gt; 435

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 4

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Arg Val Ala Lys Leu Pro Lys Asn Lys Asn Arg Asn Arg Tyr Arg Asp
35          40          45
Val Ser Pro Phe Asp His Ser Arg Ile Lys Leu His Gln Glu Asp Asn
50          55          60
Asp Tyr Ile Asn Ala Ser Leu Ile Lys Met Glu Glu Ala Gln Arg Ser
65          70          75          80
Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Gly His Phe Trp
85          90          95
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 Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly Arg Ser Gly Thr  
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 Phe Cys Leu Ala Asp Thr Cys Leu Leu Leu Met Asp Lys Arg Lys Asp  
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&lt;210&gt; 5

&lt;211&gt; 2346

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 5

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 <212> PRT  
 <213> Mus musculus

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<211> 3247
<212> DNA
<213> Homo sapiens
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&lt;210&gt; 8

&lt;211&gt; 435

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 8

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Arg Val Ala Lys Leu Pro Lys Asn Lys Asn Arg Asn Arg Tyr Arg Asp
 35            40            45
Val Ser Pro Phe Asp His Ser Arg Ile Lys Leu His Gln Glu Asp Asn
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Asp Tyr Ile Asn Ala Ser Leu Ile Lys Met Glu Glu Ala Gln Arg Ser
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Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Gly His Phe Trp
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[illegible]

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&lt;210&gt; 10

&lt;211&gt; 435

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 10

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Ala Ala Ile Tyr Gln Asp Ile Arg His Glu Ala Ser Asp Phe Pro Cys
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 Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Gly His Phe Trp  
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 Glu Met Val Trp Glu Gln Lys Ser Arg Gly Val Val Met Leu Asn Arg  
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 Ile Ser Glu Asp Ile Lys Ser Tyr Tyr Thr Val Arg Gln Leu Glu Leu  
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 Glu Asn Leu Thr Thr Gln Glu Thr Arg Glu Ile Leu His Phe His Tyr  
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 Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly Arg Ser Gly Thr  
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 Ala Val Ile Glu Gly Ala Lys Phe Ile Met Gly Asp Ser Ser Val Gln  
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 420 425 430  
 Ser Asn Thr  
 435

&lt;210&gt; 11

&lt;211&gt; 4127

&lt;212&gt; DNA

&lt;213&gt; Rattus norvegicus

&lt;400&gt; 11

```

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&lt;210&gt; 12

&lt;211&gt; 432

&lt;212&gt; PRT

&lt;213&gt; Rattus norvegicus

&lt;400&gt; 12

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20          25          30
Arg Ile Ala Lys Leu Pro Lys Asn Lys Asn Arg Asn Arg Tyr Arg Asp
35          40          45
Val Ser Pro Phe Asp His Ser Arg Ile Lys Leu His Gln Glu Asp Asn
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130         135         140
Ile Ser Glu Asp Val Lys Ser Tyr Tyr Thr Val Arg Gln Leu Glu Leu
145         150         155         160
Glu Asn Leu Ala Thr Gln Glu Ala Arg Glu Ile Leu His Phe His Tyr
165         170         175
Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe Leu
180         185         190
Asn Phe Leu Phe Lys Val Arg Glu Ser Gly Ser Leu Ser Pro Glu His
195         200         205
Gly Pro Ile Val Val His Cys Ser Ala Gly Ile Gly Arg Ser Gly Thr
210         215         220
Phe Cys Leu Ala Asp Thr Cys Leu Leu Leu Met Asp Lys Arg Lys Asp
225         230         235         240
Pro Ser Ser Val Asp Ile Lys Lys Val Leu Leu Glu Met Arg Arg Phe
245         250         255
Arg Met Gly Leu Ile Gln Thr Ala Asp Gln Leu Arg Phe Ser Tyr Leu
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275         280         285
Asp Gln Trp Lys Glu Leu Ser His Glu Asp Leu Glu Pro Pro Pro Glu
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Glu	Ser	Cys	Glu	Asp	Glu	Asp	Ile	Leu	Ala	Arg	Glu	Glu	Ser	Arg	Ala
			340					345					350		
Pro	Ser	Ile	Ala	Val	His	Ser	Met	Ser	Ser	Met	Ser	Gln	Asp	Thr	Glu
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Val	Arg	Lys	Arg	Met	Val	Gly	Gly	Gly	Leu	Gln	Ser	Ala	Gln	Ala	Ser
	370					375					380				
Val	Pro	Thr	Glu	Glu	Glu	Leu	Ser	Pro	Thr	Glu	Glu	Glu	Gln	Lys	Ala
385					390					395				400	
His	Arg	Pro	Val	His	Trp	Lys	Pro	Phe	Leu	Val	Asn	Val	Cys	Met	Ala
			405					410					415		
Thr	Ala	Leu	Ala	Thr	Gly	Ala	Tyr	Leu	Cys	Tyr	Arg	Val	Cys	Phe	His
		420						425					430		

&lt;210&gt; 13

&lt;211&gt; 2229

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 13

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<211> 597

<212> PRT

<213> Mus musculus

<400> 14

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		20						25					30		
Pro	Ser	Lys	Ser	Asn	Pro	Gly	Asp	Phe	Thr	Leu	Ser	Val	Arg	Arg	Asn
		35					40					45			
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65					70					75					80
Tyr	Met	Glu	His	His	Gly	Gln	Leu	Lys	Glu	Lys	Asn	Gly	Asp	Val	Ile
				85					90					95	
Glu	Leu	Lys	Tyr	Pro	Leu	Asn	Cys	Ala	Asp	Pro	Thr	Ser	Glu	Arg	Trp
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Phe	His	Gly	His	Leu	Ser	Gly	Lys	Glu	Ala	Glu	Lys	Leu	Leu	Thr	Glu
		115					120					125			
Lys	Gly	Lys	His	Gly	Ser	Phe	Leu	Val	Arg	Glu	Ser	Gln	Ser	His	Pro
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Asn	Asp	Gly	Lys	Ser	Lys	Val	Thr	His	Val	Met	Ile	Arg	Cys	Gln	Glu
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Leu	Lys	Tyr	Asp	Val	Gly	Gly	Gly	Glu	Arg	Phe	Asp	Ser	Leu	Thr	Asp
		180						185					190		
Leu	Val	Glu	His	Tyr	Lys	Lys	Asn	Pro	Met	Val	Glu	Thr	Leu	Gly	Thr
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Val	Leu	Gln	Leu	Lys	Gln	Pro	Leu	Asn	Thr	Thr	Arg	Ile	Asn	Ala	Ala
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	405	410
Arg Thr Val Trp Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val		415
	420	425
Pro Ser Asp Pro Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His		430
	435	440
Lys Gln Glu Ser Ile Val Asp Ala Gly Pro Val Val Val His Cys Ser		445
	450	455
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465	470	475
Asp Ile Ile Arg Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys		480
	485	490
Thr Ile Gln Met Val Arg Ser Gln Arg Ser Gly Met Val Gln Thr Glu		495
	500	505
Ala Gln Tyr Arg Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr		510
	515	520
Leu Gln Arg Arg Ile Glu Glu Glu Gln Lys Ser Lys Arg Lys Gly His		525
	530	535
Glu Tyr Thr Asn Ile Lys Tyr Ser Leu Val Asp Gln Thr Ser Gly Asp		540
545	550	555
Gln Ser Pro Leu Pro Pro Cys Thr Pro Thr Pro Pro Cys Ala Glu Met		560
	565	570
Arg Glu Asp Ser Ala Arg Val Tyr Glu Asn Val Gly Leu Met Gln Gln		575
	580	585
Gln Arg Ser Phe Arg		590
	595	

&lt;210&gt; 15

&lt;211&gt; 2236

&lt;212&gt; DNA

&lt;213&gt; Rattus norvegicus

&lt;400&gt; 15

```

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agtgagcagc ggggtccgtgc ggagccggag gcgggaggaa catgacatcc cggagatggt 120
ttcaccccaa tactactggt gtggaggcag agaatctcct gctgaccoga ggagtogatg 180
gcagtttctt agcagagccc agcaagagta accctggaga ctactactctg tctgttagaa 240
gaaatggagc cgttaccac atcaagattc agaacactgg ggactactat gacctctatg 300
gcggggaaaa gtttgccacc ttgcctgaac tgggtccagta ttacatggag catcacgggc 360
agctgaaaga gaagaatgga gatgttattg agctcaagta cccactgaac tgtgcagacc 420
ctacctctga aaggtggttc cacgggtcact tgtctggaaa agaagcagag aagctgctga 480
cagagaaggg gaagcatggc agtttcctcg tccgggagag ccagagccac cctggggact 540
tcgtcctctc cgtccgcact ggtgatgaca aaggggagag caatgacagc aagtccaaag 600
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gcacagtctt gcagctcaaa cagcccctca acacaactcg tattaatgcc gctgaaatcg 780
aaagccgggt tcgggagtta agcaagctag ccgagaccac agataaagtc aaacagggct 840
tttgggaaga atttgagact ctacagcaac aggaatgcaa acttctctac agccgaaaag 900
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gtgtcaagta ctggcctgat gagtgtgcac tcaaagagta tggcgtcatg cgtgtgagga 1260

```



```

acgtcagaga aagtgtctgcg catgactaca ccttacgaga actcaaactc tctaagggtcg 1320
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gtgtgcctag tgaccttggg ggtgtgctgg acttcctgga ggagggtccac cacaagcagg 1440
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cagaagcaca gtaccggttc atctacatgg cgtccagca ctacatagag acgtgtcaac 1680
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agacctgtta agaccg 2236

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&lt;210&gt; 16

&lt;211&gt; 593

&lt;212&gt; PRT

&lt;213&gt; Rattus norvegicus

&lt;400&gt; 16

```

Met Thr Ser Arg Arg Trp Phe His Pro Asn Ile Thr Gly Val Glu Ala
 1             5             10             15
Glu Asn Leu Leu Leu Thr Arg Gly Val Asp Gly Ser Phe Leu Ala Arg
      20             25             30
Pro Ser Lys Ser Asn Pro Gly Asp Phe Thr Leu Ser Val Arg Arg Asn
      35             40             45
Gly Ala Val Thr His Ile Lys Ile Gln Asn Thr Gly Asp Tyr Tyr Asp
      50             55             60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Pro Glu Leu Val Gln Tyr
      65             70             75             80
Tyr Met Glu His His Gly Gln Leu Lys Glu Lys Asn Gly Asp Val Ile
      85             90             95
Glu Leu Lys Tyr Pro Leu Asn Cys Ala Asp Pro Thr Ser Glu Arg Trp
      100            105            110
Phe His Gly His Leu Ser Gly Lys Glu Ala Glu Lys Leu Leu Thr Glu
      115            120            125
Lys Gly Lys His Gly Ser Phe Leu Val Arg Glu Ser Gln Ser His Pro
      130            135            140
Gly Asp Phe Val Leu Ser Val Arg Thr Gly Asp Asp Lys Gly Glu Ser
      145            150            155            160
Asn Asp Ser Lys Ser Lys Val Thr His Val Met Ile Arg Cys Gln Glu
      165            170            175
Leu Lys Tyr Asp Val Gly Gly Gly Glu Arg Phe Asp Ser Leu Thr Asp
      180            185            190
Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr
      195            200            205
Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala
      210            215            220
Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr
      225            230            235            240
Asp Lys Val Lys Gln Gly Phe Trp Glu Glu Phe Glu Thr Leu Gln Gln
      245            250            255
Gln Glu Cys Lys Leu Leu Tyr Ser Arg Lys Glu Gly Gln Arg Gln Glu
      260            265            270

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Asn	Lys	Asn	Lys	Asn	Arg	Tyr	Lys	Asn	Ile	Leu	Pro	Phe	Asp	His	Thr
	275						280					285			
Arg	Val	Val	Leu	His	Asp	Gly	Asp	Pro	Asn	Glu	Pro	Val	Ser	Asp	Tyr
	290					295					300				
Ile	Asn	Ala	Asn	Ile	Ile	Met	Pro	Glu	Phe	Glu	Thr	Lys	Cys	Asn	Asn
305					310					315					320
Ser	Lys	Pro	Lys	Lys	Ser	Tyr	Ile	Ala	Thr	Gln	Gly	Cys	Leu	Gln	Asn
				325					330					335	
Thr	Val	Asn	Asp	Phe	Trp	Arg	Met	Val	Phe	Gln	Glu	Asn	Ser	Arg	Val
			340					345					350		
Ile	Val	Met	Thr	Thr	Lys	Glu	Val	Glu	Arg	Gly	Lys	Ser	Lys	Cys	Val
		355					360					365			
Lys	Tyr	Trp	Pro	Asp	Glu	Cys	Ala	Leu	Lys	Glu	Tyr	Gly	Val	Met	Arg
	370					375					380				
Val	Arg	Asn	Val	Arg	Glu	Ser	Ala	Ala	His	Asp	Tyr	Thr	Leu	Arg	Glu
385						390				395					400
Leu	Lys	Leu	Ser	Lys	Val	Gly	Gln	Gly	Asn	Thr	Glu	Arg	Thr	Val	Trp
				405					410					415	
Gln	Tyr	His	Phe	Arg	Thr	Trp	Pro	Asp	His	Gly	Val	Pro	Ser	Asp	Pro
			420					425					430		
Gly	Gly	Val	Leu	Asp	Phe	Leu	Glu	Glu	Val	His	His	Lys	Gln	Glu	Ser
		435					440					445			
Ile	Val	Asp	Ala	Gly	Pro	Val	Val	Val	His	Cys	Ser	Ala	Gly	Ile	Gly
	450					455					460				
Arg	Thr	Gly	Thr	Phe	Ile	Val	Ile	Asp	Ile	Leu	Ile	Asp	Ile	Ile	Arg
465					470					475					480
Glu	Lys	Gly	Val	Asp	Cys	Asp	Ile	Asp	Val	Pro	Lys	Thr	Ile	Gln	Met
				485				490						495	
Val	Arg	Ser	Gln	Arg	Ser	Gly	Met	Val	Gln	Thr	Glu	Ala	Gln	Tyr	Arg
			500					505					510		
Phe	Ile	Tyr	Met	Ala	Val	Gln	His	Tyr	Ile	Glu	Thr	Leu	Gln	Arg	Arg
		515					520					525			
Ile	Glu	Glu	Gln	Lys	Ser	Lys	Arg	Lys	Gly	His	Glu	Tyr	Thr	Asn	
	530				535					540					
Ile	Lys	Tyr	Ser	Leu	Val	Asp	Gln	Thr	Ser	Gly	Asp	Gln	Ser	Pro	Leu
545					550					555					560
Pro	Pro	Cys	Thr	Pro	Thr	Pro	Pro	Cys	Ala	Glu	Met	Arg	Glu	Asp	Ser
				565					570					575	
Ala	Arg	Val	Tyr	Glu	Asn	Val	Gly	Leu	Met	Gln	Gln	Gln	Arg	Ser	Phe
			580					585					590		

Arg

&lt;210&gt; 17

&lt;211&gt; 2287

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 17

```

ggggggcctg agcctctccg cgggcgcagg ctctgctcgc gccagctcgc tcccgcagcc 60
atgcccacca ccatcgagcg ggagttcgaa gagttggata ctcagcgtcg ctggcagccg 120
ctgtacttgg aaattcgaaa tgagtcccat gactatcctc atagagtggc caagtttcca 180
gaaaacagaa atcgaaacag atacagagat gtaagcccat atgatcacag tcgtgtttaa 240
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aggagttaca tcttaacaca ggggtccactt cctaacacat gctgccattt ctggccttatg 360
gtttggcagc agaagaccaa agcagttgtc atgctgaacc gcattgtgga gaaagaatcg 420
gttaaattgtg cacagtactg gccaacagat gaccaagaga tgctgtttta agaaacagga 480

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ttagaaaata tcaatagtgg tgaaccaga acaatatctc actttcatta tactacctgg 600
ccagattttg gagtccctga atcaccagct tcatttctca atttcttggt taaagtgaga 660
gaatctggct ccttgaaccc tgaccatggg cctgcggtga tccactgtag tgcaggcatt 720
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gatattaaca taaaacaagt gttactgaac atgagaaaaat accgaatggg tcttattcag 840
accccagatc aactgagatt ctcatatcat gctataatag aaggagcaaa atgtataaag 900
ggagattcta gtatacagaa acgatggaaa gaactttcta aggaagactt atctcctgcc 960
tttgatcatt caccaaacaa aataatgact gaaaaataca atgggaacag aataggtcta 1020
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gcccagcaag cttctgcact agtaactgac agtgctacat taatcatagg ggtttgtctg 1380
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taaacc

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&lt;210&gt; 18

&lt;211&gt; 415

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 18

```

Met Pro Thr Thr Ile Glu Arg Glu Phe Glu Glu Leu Asp Thr Gln Arg
1           5           10           15
Arg Trp Gln Pro Leu Tyr Leu Glu Ile Arg Asn Glu Ser His Asp Tyr
20           25           30
Pro His Arg Val Ala Lys Phe Pro Glu Asn Arg Asn Arg Asn Arg Tyr
35           40           45
Arg Asp Val Ser Pro Tyr Asp His Ser Arg Val Lys Leu Gln Asn Ala
50           55           60
Glu Asn Asp Tyr Ile Asn Ala Ser Leu Val Asp Ile Glu Glu Ala Gln
65           70           75           80
Arg Ser Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Cys His
85           90           95
Phe Trp Leu Met Val Trp Gln Gln Lys Thr Lys Ala Val Val Met Leu
100          105          110
Asn Arg Ile Val Glu Lys Glu Ser Val Lys Cys Ala Gln Tyr Trp Pro
115          120          125
Thr Asp Asp Gln Glu Met Leu Phe Lys Glu Thr Gly Phe Ser Val Lys
130          135          140
Leu Leu Ser Glu Asp Val Lys Ser Tyr Tyr Thr Val His Leu Leu Gln
145          150          155          160

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Leu Glu Asn Ile Asn Ser Gly Glu Thr Arg Thr Ile Ser His Phe His  
 165 170 175  
 Tyr Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe  
 180 185 190  
 Leu Asn Phe Leu Phe Lys Val Arg Glu Ser Gly Ser Leu Asn Pro Asp  
 195 200 205  
 His Gly Pro Ala Val Ile His Cys Ser Ala Gly Ile Gly Arg Ser Gly  
 210 215 220  
 Thr Phe Ser Leu Val Asp Thr Cys Leu Val Leu Met Glu Lys Gly Asp  
 225 230 235 240  
 Asp Ile Asn Ile Lys Gln Val Leu Leu Asn Met Arg Lys Tyr Arg Met  
 245 250 255  
 Gly Leu Ile Gln Thr Pro Asp Gln Leu Arg Phe Ser Tyr Met Ala Ile  
 260 265 270  
 Ile Glu Gly Ala Lys Cys Ile Lys Gly Asp Ser Ser Ile Gln Lys Arg  
 275 280 285  
 Trp Lys Glu Leu Ser Lys Glu Asp Leu Ser Pro Ala Phe Asp His Ser  
 290 295 300  
 Pro Asn Lys Ile Met Thr Glu Lys Tyr Asn Gly Asn Arg Ile Gly Leu  
 305 310 315 320  
 Glu Glu Glu Lys Leu Thr Gly Asp Arg Cys Thr Gly Leu Ser Ser Lys  
 325 330 335  
 Met Gln Asp Thr Met Glu Glu Asn Ser Glu Ser Ala Leu Arg Lys Arg  
 340 345 350  
 Ile Arg Glu Asp Arg Lys Ala Thr Thr Ala Gln Lys Val Gln Gln Met  
 355 360 365  
 Lys Gln Arg Leu Asn Glu Asn Glu Arg Lys Arg Lys Arg Trp Leu Tyr  
 370 375 380  
 Trp Gln Pro Ile Leu Thr Lys Met Gly Phe Met Ser Val Ile Leu Val  
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 Gly Ala Phe Val Gly Trp Arg Leu Phe Phe Gln Gln Asn Ala Leu  
 405 410 415

<210> 19  
 <211> 462  
 <212> DNA  
 <213> Homo sapiens

<400> 19  
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 tcatgactta agaatattct gcagctataa attttgaacc attgatgtgc aaagcaagac 180  
 ctgaagccca ctccggaac taaagtgagg ctcgctaacc ctctagattg cctcacagtt 240  
 gtttgtttac aaagtaaact ttacatccag gggatgaaga gcacccacca gcagaagact 300  
 ttgcagaacc tttaattgga tgtgttaagt gtttttaagt agtgtatgaa atgtagaaag 360  
 atgtacaaga aataaattag gagagattac tttgtattgt actgccattc ctactgtatt 420  
 ttatacttt ttggcagcat taaatatttt tgttaaataag tc 462

<210> 20  
 <211> 462  
 <212> DNA  
 <213> Homo sapiens

<400> 20  
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 cagaggctaa atgagaatga acgaaaaaga aaaaggccaa gattgacaga cacctaatat 120  
 tcatgactta agaatattct gcagctataa attttgaacc attgatgtgc aaagcaagac 180

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ctgaagccca ctccggaaac taaagtgagg ctcgctaacc ctctagattg cctcacagtt 240
gtttgtttac aaagtaaaac ttacatccag gggatgaaga gcaccacca gcagaagact 300
ttgcagaacc ttttaattgga tgtgttaagt gtttttaagt agtgtatgaa atgtagaag 360
atgtacaaga aataaattag gagagattac tttgtattgt actgccattc ctactgtatt 420
tttatacttt ttggcagcat taaatatttt tgtaaataag tc 462

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&lt;210&gt; 21

&lt;211&gt; 1555

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 21

```

tctccccgga tagagcgggg cccgagcctg tccgctgtgg tagttccgct cggctgcccc 60
gccgccatgt cggcaaccat cgagcgggag ttcgaggaac tggatgctca gtgtcgctgg 120
cagccgttat acttggaat tcgaaatgaa tcccatgact atcctcatag agtggccaag 180
tttccagaaa acagaaaccg aaacagatac agagatgtaa gcccatatga tcacagtcgt 240
gttaaaactgc aaagtactga aaatgattat attaatgccg gcttagttga catagaagag 300
gcacaaagaa gttacatctt aacacagggc ccacttccga acacatgctg ccatttctgg 360
ctcatggtgt ggcagcaaaa gaccaaagca gttgtcatgc taaaccgaac tgtagaaaaa 420
gaatcggtta aatgtgcaca gtactggcca acggatgaca gagaaatggg gtttaaggaa 480
acgggattca gtgtgaagct cttatctgaa gatgtaaaat catattatac agtacatcta 540
ctacagttag aaaatatcaa tactggtgaa acgagaacca tatctcactt ccattatacc 600
acctggccag attttggggg tccagagtca ccagcttcat ttctaaactt cttgtttaaa 660
gttagagaat ctggttgttt gaccctgac catggacctg cagtgatcca ttgcagtgcg 720
ggcatcgggc gctctggcac cttctctctt gtagatacct gtcttgttct gatggaaaaa 780
ggagaggatg ttaatgtgaa acaattatta ctgaatatga gaaagtatcg aatgggactt 840
attcagacac cggaccaact cagattctcc tacatggcca taatagaagg agcaaagtac 900
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cattcctaatt gtattttttat actttttggc agcattaaat atttttatta aatag 1555

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&lt;210&gt; 22

&lt;211&gt; 382

&lt;212&gt; PRT

&lt;213&gt; Mus musculus

&lt;400&gt; 22

```

Met Ser Ala Thr Ile Glu Arg Glu Phe Glu Glu Leu Asp Ala Gln Cys
 1           5           10          15
Arg Trp Gln Pro Leu Tyr Leu Glu Ile Arg Asn Glu Ser His Asp Tyr
          20          25          30
Pro His Arg Val Ala Lys Phe Pro Glu Asn Arg Asn Arg Asn Arg Tyr
          35          40          45
Arg Asp Val Ser Pro Tyr Asp His Ser Arg Val Lys Leu Gln Ser Thr
          50          55          60
Glu Asn Asp Tyr Ile Asn Ala Ser Leu Val Asp Ile Glu Glu Ala Gln
          65          70          75          80
Arg Ser Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Cys His
          85          90          95
Phe Trp Leu Met Val Trp Gln Gln Lys Thr Lys Ala Val Val Met Leu

```

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aagtatcgaa	tgggactcat	tcagactcgg	gaccagctca	gattctccta	catggccata	840
atagaaggag	caaagtatac	aaaaggagat	tcaaataatac	agaacagaac	aatgactgag	900

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&lt;210&gt; 24

&lt;211&gt; 363

&lt;212&gt; PRT

&lt;213&gt; Rattus norvegicus

&lt;400&gt; 24

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Met Ser Ala Thr Ile Glu Arg Glu Phe Glu Glu Leu Asp Ala Gln Cys
 1             5             10             15
Arg Trp Gln Pro Leu Tyr Leu Glu Ile Arg Asn Glu Ser His Asp Tyr
 20             25             30
Pro His Arg Val Ala Lys Phe Pro Glu Asn Arg Asn Arg Asn Arg Tyr
 35             40             45
Arg Asp Val Ser Pro Tyr Asp His Ser Arg Val Lys Leu Gln Ser Ala
 50             55             60
Glu Asn Asp Tyr Ile Asn Ala Ser Leu Val Asp Ile Glu Glu Ala Gln
 65             70             75             80
Arg Ser Tyr Ile Leu Thr Gln Gly Pro Leu Pro Asn Thr Cys Cys His
 85             90             95
Phe Trp Leu Met Val Trp Gln Gln Lys Thr Arg Ala Val Val Met Leu
100            105            110
Asn Arg Thr Val Glu Lys Glu Ser Val Lys Cys Ala Gln Tyr Trp Pro
115            120            125
Thr Asp Asp Arg Glu Met Val Phe Lys Glu Thr Gly Phe Ser Val Lys
130            135            140
Leu Leu Ser Glu Asp Val Lys Ser Tyr Tyr Thr Val His Leu Leu Gln
145            150            155            160
Leu Glu Asn Ile Asn Ser Gly Glu Thr Arg Thr Ile Ser His Phe His
165            170            175
Tyr Thr Thr Trp Pro Asp Phe Gly Val Pro Glu Ser Pro Ala Ser Phe
180            185            190
Leu Asn Phe Leu Phe Lys Val Arg Glu Ser Gly Ser Leu Asn Pro Asp
195            200            205
His Gly Pro Ala Val Ile His Cys Ser Ala Gly Ile Gly Arg Ser Gly
210            215            220
Thr Phe Ser Leu Val Asp Thr Cys Leu Val Leu Met Glu Lys Gly Glu
225            230            235            240
Asp Val Asn Val Lys Gln Ile Leu Leu Ser Met Arg Lys Tyr Arg Met
245            250            255
Gly Leu Ile Gln Thr Pro Asp Gln Leu Arg Phe Ser Tyr Met Ala Ile
260            265            270
Ile Glu Gly Ala Lys Tyr Thr Lys Gly Asp Ser Asn Ile Gln Asn Arg
275            280            285
Thr Met Thr Glu Lys Tyr Asn Gly Lys Arg Ile Gly Ser Glu Asp Glu
290            295            300
Lys Leu Thr Gly Leu Ser Ser Lys Val Pro Asp Thr Val Glu Glu Ser
305            310            315            320
Ser Glu Ser Ile Leu Arg Lys Arg Ile Arg Glu Asp Arg Lys Ala Thr

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			325					330				335			
Thr	Ala	Gln	Lys	Val	Gln	Gln	Met	Arg	Gln	Arg	Leu	Asn	Glu	Thr	Glu
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Arg	Lys	Arg	Lys	Arg	Pro	Arg	Leu	Thr	Asp	Thr					
			355				360								

<210> 25  
 <211> 2543  
 <212> DNA  
 <213> Homo sapiens

<400> 25

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agcgggtccg	tcgcggagcc	ggagggcggg	aggaacatga	catcgcgggag	atggtttcac	180
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<210> 26



<211> 593  
 <212> PRT  
 <213> Homo sapiens

<400> 26

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      20      25      30
Pro Ser Lys Ser Asn Pro Gly Asp Phe Thr Leu Ser Val Arg Arg Asn
      35      40      45
Gly Ala Val Thr His Ile Lys Ile Gln Asn Thr Gly Asp Tyr Tyr Asp
      50      55      60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Ala Glu Leu Val Gln Tyr
      65      70      75      80
Tyr Met Glu His His Gly Gln Leu Lys Glu Lys Asn Gly Asp Val Ile
      85      90      95
Glu Leu Lys Tyr Pro Leu Asn Cys Ala Asp Pro Thr Ser Glu Arg Trp
      100      105      110
Phe His Gly His Leu Ser Gly Lys Glu Ala Glu Lys Leu Leu Thr Glu
      115      120      125
Lys Gly Lys His Gly Ser Phe Leu Val Arg Glu Ser Gln Ser His Pro
      130      135      140
Gly Asp Phe Val Leu Ser Val Arg Thr Gly Asp Asp Lys Gly Glu Ser
      145      150      155      160
Asn Asp Gly Lys Ser Lys Val Thr His Val Met Ile Arg Cys Gln Glu
      165      170      175
Leu Lys Tyr Asp Val Gly Gly Gly Glu Arg Phe Asp Ser Leu Thr Asp
      180      185      190
Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr
      195      200      205
Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala
      210      215      220
Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr
      225      230      235      240
Asp Lys Val Lys Gln Gly Phe Trp Glu Glu Phe Glu Thr Leu Gln Gln
      245      250      255
Gln Glu Cys Lys Leu Leu Tyr Ser Arg Lys Glu Gly Gln Arg Gln Glu
      260      265      270
Asn Lys Asn Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Thr
      275      280      285
Arg Val Val Leu His Asp Gly Asp Pro Asn Glu Pro Val Ser Asp Tyr
      290      295      300
Ile Asn Ala Asn Ile Ile Met Pro Glu Phe Glu Thr Lys Cys Asn Asn
      305      310      315      320
Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn
      325      330      335
Thr Val Asn Asp Phe Trp Arg Met Val Phe Gln Glu Asn Ser Arg Val
      340      345      350
Ile Val Met Thr Thr Lys Glu Val Glu Arg Gly Lys Ser Lys Cys Val
      355      360      365
Lys Tyr Trp Pro Asp Glu Tyr Ala Leu Lys Glu Tyr Gly Val Met Arg
      370      375      380
Val Arg Asn Val Lys Glu Ser Ala Ala His Asp Tyr Thr Leu Arg Glu
      385      390      395      400
Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp
      405      410      415
Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro
  
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Ile Met Asp	Ala Gly Pro Val Val	His Cys Ser Ala	Gly Ile Gly		
	450		455		460
Arg Thr Gly	Thr Phe Ile Val Ile	Asp Ile Leu Ile	Asp Ile Ile	Arg	
465		470		475	480
Glu Lys Gly	Val Asp Cys Asp Ile	Asp Val Pro Lys	Thr Ile Gln	Met	
	485		490		495
Val Arg Ser	Gln Arg Ser Gly Met	Val Gln Thr Glu	Ala Gln Tyr	Arg	
	500		505		510
Phe Ile Tyr	Met Ala Val Gln His	Tyr Ile Glu Thr	Leu Gln Arg	Arg	
	515		520		525
Ile Glu Glu	Glu Gln Lys Arg Lys	Arg Lys Gly His	Glu Tyr Thr	Asn	
	530		535		540
Ile Lys Tyr	Pro Leu Ala Asp Gln	Thr Ser Gly Asp	Gln Ser Pro	Leu	
545		550		555	560
Pro Pro Cys	Thr Pro Thr Pro	Cys Ala Glu Met	Arg Glu Asp	Ser	
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Ala Arg Val	Tyr Glu Asn Val Gly	Leu Met Gln Gln	Gln Lys Ser	Phe	
	580		585		590

Arg

<210> 27  
 <211> 2276  
 <212> DNA  
 <213> Homo sapiens

<400> 27

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<210> 28  
 <211> 593  
 <212> PRT  
 <213> Homo sapiens

<400> 28

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			20					25					30		
Pro	Ser	Lys	Ser	Asn	Pro	Gly	Asp	Phe	Thr	Leu	Ser	Val	Arg	Arg	Asn
		35					40					45			
Gly	Ala	Val	Thr	His	Ile	Lys	Ile	Gln	Asn	Thr	Gly	Asp	Tyr	Tyr	Asp
	50					55					60				
Leu	Tyr	Gly	Gly	Glu	Lys	Phe	Ala	Thr	Leu	Ala	Glu	Leu	Val	Gln	Tyr
65					70					75				80	
Tyr	Met	Glu	His	His	Gly	Gln	Leu	Lys	Glu	Lys	Asn	Gly	Asp	Val	Ile
				85					90					95	
Glu	Leu	Lys	Tyr	Pro	Leu	Asn	Cys	Ala	Asp	Pro	Thr	Ser	Glu	Arg	Trp
			100					105					110		
Phe	His	Gly	His	Leu	Ser	Gly	Lys	Glu	Ala	Glu	Lys	Leu	Leu	Thr	Glu
		115					120					125			
Lys	Gly	Lys	His	Gly	Ser	Phe	Leu	Val	Arg	Glu	Ser	Gln	Ser	His	Pro
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Gly	Asp	Phe	Val	Leu	Ser	Val	Arg	Thr	Gly	Asp	Asp	Lys	Gly	Glu	Ser
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Asn	Asp	Gly	Lys	Ser	Lys	Val	Thr	His	Val	Met	Ile	Arg	Cys	Gln	Glu
			165						170					175	
Leu	Lys	Tyr	Asp	Val	Gly	Gly	Gly	Glu	Arg	Phe	Asp	Ser	Leu	Thr	Asp
			180					185					190		
Leu	Val	Glu	His	Tyr	Lys	Lys	Asn	Pro	Met	Val	Glu	Thr	Leu	Gly	Thr
		195					200					205			
Val	Leu	Gln	Leu	Lys	Gln	Pro	Leu	Asn	Thr	Thr	Arg	Ile	Asn	Ala	Ala
	210					215					220				
Glu	Ile	Glu	Ser	Arg	Val	Arg	Glu	Leu	Ser	Lys	Leu	Ala	Glu	Thr	Thr
225					230					235				240	
Asp	Lys	Val	Lys	Gln	Gly	Phe	Trp	Glu	Glu	Phe	Glu	Thr	Leu	Gln	Gln
			245						250					255	
Gln	Glu	Cys	Lys	Leu	Leu	Tyr	Ser	Arg	Lys	Glu	Gly	Gln	Arg	Gln	Glu
			260					265					270		
Asn	Lys	Asn	Lys	Asn	Arg	Tyr	Lys	Asn	Ile	Leu	Pro	Phe	Asp	His	Thr
		275					280					285			
Arg	Val	Val	Leu	His	Asp	Gly	Asp	Pro	Asn	Glu	Pro	Val	Ser	Asp	Tyr
	290					295					300				
Ile	Asn	Ala	Asn	Ile	Ile	Met	Pro	Glu	Phe	Glu	Thr	Lys	Cys	Asn	Asn
305				310						315					320

Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn  
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 Ile Val Met Thr Thr Lys Glu Val Glu Arg Gly Lys Ser Lys Cys Val  
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 Lys Tyr Trp Pro Asp Glu Tyr Ala Leu Lys Glu Tyr Gly Val Met Arg  
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 Leu Lys Leu Ser Lys Val Gly Gln Gly Asn Thr Glu Arg Thr Val Trp  
 405 410 415  
 Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro  
 420 425 430  
 Gly Gly Val Leu Asp Phe Leu Glu Glu Val His His Lys Gln Glu Ser  
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 Ile Met Asp Ala Gly Pro Val Val Val His Cys Ser Ala Gly Ile Gly  
 450 455 460  
 Arg Thr Gly Thr Phe Ile Val Ile Asp Ile Leu Ile Asp Ile Ile Arg  
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 Glu Lys Gly Val Asp Cys Asp Ile Asp Val Pro Lys Thr Ile Gln Met  
 485 490 495  
 Val Arg Ser Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Arg  
 500 505 510  
 Phe Ile Tyr Met Ala Val Gln His Tyr Ile Glu Thr Leu Gln Arg Arg  
 515 520 525  
 Ile Glu Glu Glu Gln Lys Ser Lys Arg Lys Gly His Glu Tyr Thr Asn  
 530 535 540  
 Ile Lys Tyr Ser Leu Ala Asp Gln Thr Ser Gly Asp Gln Ser Pro Leu  
 545 550 555 560  
 Pro Pro Cys Thr Pro Thr Pro Pro Cys Ala Glu Met Arg Glu Asp Ser  
 565 570 575  
 Ala Arg Val Tyr Glu Asn Val Gly Leu Met Gln Gln Gln Lys Ser Phe  
 580 585 590  
 Arg

&lt;210&gt; 29

&lt;211&gt; 2121

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 29

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&lt;210&gt; 30

&lt;211&gt; 593

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 30

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Glu Asn Leu Leu Thr Arg Gly Val Asp Gly Ser Phe Leu Ala Arg
20          25          30
Pro Ser Lys Ser Asn Pro Gly Asp Phe Thr Leu Ser Val Arg Arg Asn
35          40          45
Gly Ala Val Thr His Ile Lys Ile Gln Asn Thr Gly Asp Tyr Tyr Asp
50          55          60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Ala Glu Leu Val Gln Tyr
65          70          75          80
Tyr Met Glu His His Gly Gln Leu Lys Glu Lys Asn Gly Asp Val Ile
85          90          95
Glu Leu Lys Tyr Pro Leu Asn Cys Ala Asp Pro Thr Ser Glu Arg Trp
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Phe His Gly His Leu Ser Gly Lys Glu Ala Glu Lys Leu Leu Thr Glu
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130          135          140
Gly Asp Phe Val Leu Ser Val Arg Thr Gly Asp Asp Lys Gly Glu Ser
145          150          155          160
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165          170          175
Leu Lys Tyr Asp Val Gly Gly Gly Glu Arg Phe Asp Ser Leu Thr Asp
180          185          190
Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr
195          200          205
Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala
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Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr

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Ile	Asn	Ala	Asn	Ile	Ile	Met	Pro	Glu	Phe	Glu	Thr	Lys	Cys	Asn	Asn
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Ser	Lys	Pro	Lys	Lys	Ser	Tyr	Ile	Ala	Thr	Gln	Gly	Cys	Leu	Gln	Asn
				325				330					335		
Thr	Val	Asn	Asp	Phe	Trp	Arg	Met	Val	Phe	Gln	Glu	Asn	Ser	Arg	Val
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Gln	Tyr	His	Phe	Arg	Thr	Trp	Pro	Asp	His	Gly	Val	Pro	Ser	Asp	Pro
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Gly	Gly	Val	Leu	Asp	Phe	Leu	Glu	Glu	Val	His	His	Lys	Gln	Glu	Ser
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Pro	Pro	Cys	Thr	Pro	Thr	Pro	Pro	Cys	Ala	Glu	Met	Arg	Glu	Asp	Ser
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 <211> 1980  
 <212> DNA  
 <213> Homo sapiens

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<210> 32

<211> 593

<212> PRT

<213> Homo sapiens

<400> 32

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Pro Ser Lys Ser Asn Pro Gly Asp Phe Thr Leu Ser Val Arg Arg Asn
          35          40          45
Gly Ala Val Thr His Ile Lys Ile Gln Asn Thr Gly Asp Tyr Tyr Asp
          50          55          60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Ala Glu Leu Val Gln Tyr
65             70             75             80
Tyr Met Glu His His Gly Gln Leu Lys Glu Lys Asn Gly Asp Val Ile
          85          90          95
Glu Leu Lys Tyr Pro Leu Asn Cys Ala Asp Pro Thr Ser Glu Arg Trp
          100         105         110
Phe His Gly His Leu Ser Gly Lys Glu Ala Glu Lys Leu Leu Thr Glu
          115         120         125
Lys Gly Lys His Gly Ser Phe Leu Val Arg Glu Ser Gln Ser His Pro
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Gly Asp Phe Val Leu Ser Val Arg Thr Gly Asp Asp Lys Gly Glu Ser
145             150             155             160

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 Leu Val Glu His Tyr Lys Lys Asn Pro Met Val Glu Thr Leu Gly Thr  
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 Val Leu Gln Leu Lys Gln Pro Leu Asn Thr Thr Arg Ile Asn Ala Ala  
 210 215 220  
 Glu Ile Glu Ser Arg Val Arg Glu Leu Ser Lys Leu Ala Glu Thr Thr  
 225 230 235 240  
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 305 310 315 320  
 Ser Lys Pro Lys Lys Ser Tyr Ile Ala Thr Gln Gly Cys Leu Gln Asn  
 325 330 335  
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 <213> Homo sapiens

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 Gln Tyr His Phe Arg Thr Trp Pro Asp His Gly Val Pro Ser Asp Pro  
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<210> 36  
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 <212> DNA  
 <213> Homo sapiens

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&lt;210&gt; 38

&lt;211&gt; 913

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 38

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Ile His Phe Leu Asp Gly Val Val Gln Thr Phe Lys Val Thr Lys Gln
          35          40          45
Asp Thr Gly Gln Val Leu Leu Asp Met Val His Asn His Leu Gly Val

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Gly	Gly	Phe	Pro	Cys	Thr	Leu	His	Phe	Arg	Val	Arg	Phe	Phe	Ile	Pro		
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Asp	Pro	Asn	Thr	Leu	Gln	Gln	Glu	Gln	Thr	Arg	His	Leu	Tyr	Phe	Leu		
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Gln	Leu	Lys	Met	Asp	Ile	Cys	Glu	Gly	Arg	Leu	Thr	Cys	Pro	Leu	Asn		
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Arg	Asp	Leu	His	Asn	Leu	Asp	Leu	Met	Ile	Gly	Ile	Ala	Ser	Ala	Gly		
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Val	Ala	Val	Tyr	Arg	Lys	Tyr	Ile	Cys	Thr	Ser	Phe	Tyr	Pro	Trp	Val		
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Arg	Gln	Lys	Gln	Ala	Glu	Ser	Arg	Glu	His	Ile	Val	Ala	Phe	Asn	Met		
		275					280					285					
Leu	Asn	Tyr	Arg	Ser	Cys	Lys	Asn	Leu	Trp	Lys	Ser	Cys	Val	Glu	His		
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Pro	Ser	Arg	Ser	Pro	Pro	Ile	Thr	Pro	Asn	Trp	Arg	Ser	Pro	Arg	Leu		
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Arg	His	Glu	Ile	Arg	Lys	Pro	Arg	His	Ser	Ser	Ala	Asp	Asn	Leu	Ala		
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Met Phe Ile Lys Ala Ser Arg Glu Ser His Ser Arg Glu Leu Ala Leu		
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Val Ile Arg Arg Arg Ala Val Arg Ser Phe Ala Asp Phe Lys Ser Glu		
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Asp Glu Leu Asn Gln Leu Phe Pro Glu Ala Ile Phe Pro Met Cys Pro		
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Glu Gly Gly Asp Thr Leu Glu Gly Ser Met Ala Gln Leu Lys Lys Gly		
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Lys Pro Gly Leu Ala Ile Thr Phe Ala Lys Leu Pro Gln Asn Leu Asp		
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Ile Pro Ala Ala Asn Leu Val Asn Lys Tyr Ile Ala Thr Gln Gly Pro		
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Leu Pro His Thr Cys Ala Gln Phe Trp Gln Val Val Trp Asp Gln Lys		
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Leu Ser Leu Ile Val Met Leu Thr Thr Leu Thr Glu Arg Gly Arg Thr		
740	745	750
Lys Cys His Gln Tyr Trp Pro Asp Pro Pro Asp Val Met Asn His Gly		
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Gly Phe His Ile Gln Cys Gln Ser Glu Asp Cys Thr Ile Ala Tyr Val		
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Ser Arg Glu Met Leu Val Thr Asn Thr Gln Thr Gly Glu Glu His Thr		
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Ser		

&lt;210&gt; 39

&lt;211&gt; 2111

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 39

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&lt;210&gt; 40

&lt;211&gt; 703

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 40

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Asp Leu His Asn Leu Asp Leu Met Ile Gly Ile Ala Ser Ala Gly Val
35           40           45
Ala Val Tyr Arg Lys Tyr Ile Cys Thr Ser Phe Tyr Pro Trp Val Asn
50           55           60
Ile Leu Lys Ile Ser Phe Lys Arg Lys Lys Phe Phe Ile His Gln Arg
65           70           75           80
Gln Lys Gln Ala Glu Ser Arg Glu His Ile Val Ala Phe Asn Met Leu
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Asn Tyr Arg Ser Cys Lys Asn Leu Trp Lys Ser Cys Val Glu His His
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 Glu Met Thr Tyr Ile Thr Glu Thr Glu Asp Val Phe Tyr Thr Tyr Lys  
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 Gly Ser Leu Ala Pro Gln Asp Ser Asp Ser Glu Val Ser Gln Asn Arg  
 225 230 235 240  
 Ser Pro His Gln Glu Ser Leu Ser Glu Asn Asn Pro Ala Gln Ser Tyr  
 245 250 255  
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 Pro His Thr Cys Ala Gln Phe Trp Gln Val Val Trp Asp Gln Lys Leu  
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 Ser Leu Ile Val Met Leu Thr Thr Leu Thr Glu Arg Gly Arg Thr Lys  
 545 550 555 560  
 Cys His Gln Tyr Trp Pro Asp Pro Pro Asp Val Met Asn His Gly Gly  
 565 570 575

Phe His Ile Gln Cys Gln Ser Glu Asp Cys Thr Ile Ala Tyr Val Ser  
 580 585 590  
 Arg Glu Met Leu Val Thr Asn Thr Gln Thr Gly Glu Glu His Thr Val  
 595 600 605  
 Thr His Leu Gln Tyr Val Ala Trp Pro Asp His Gly Ile Pro Asp Asp  
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 <213> Homo sapiens

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<210> 42  
 <211> 1337  
 <212> PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 42

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Ile Leu Cys Ala Gly Gly Thr Pro Ser Pro Ile Pro Asp Pro Ser Val
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Ala Thr Val Ala Thr Gly Glu Asn Gly Ile Thr Gln Ile Ser Ser Thr
      50           55           60
Ala Glu Ser Phe His Lys Gln Asn Gly Thr Gly Thr Pro Gln Val Glu
65           70           75           80
Thr Asn Thr Ser Glu Asp Gly Glu Ser Ser Gly Ala Asn Asp Ser Leu
      85           90           95
Arg Thr Pro Glu Gln Gly Ser Asn Gly Thr Asp Gly Ala Ser Gln Lys
      100          105          110
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Ser Ile Ser Pro Thr Asn Val Ile Leu Thr Trp Lys Ser Asn Asp Thr
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Ala Ala Ser Glu Tyr Lys Tyr Val Val Lys His Lys Met Glu Asn Glu
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Lys Thr Ile Thr Val Val His Gln Pro Trp Cys Asn Ile Thr Gly Leu
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Arg Pro Ala Thr Ser Tyr Val Phe Ser Ile Thr Pro Gly Ile Gly Asn
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Glu Thr Trp Gly Asp Pro Arg Val Ile Lys Val Ile Thr Glu Pro Ile
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Pro Val Ser Asp Leu Arg Val Ala Leu Thr Gly Val Arg Lys Ala Ala
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Leu Ser Trp Ser Asn Gly Asn Gly Thr Ala Ser Cys Arg Val Leu Leu
225          230          235          240
Glu Ser Ile Gly Ser His Glu Glu Leu Thr Gln Asp Ser Arg Leu Gln
      245          250          255
Val Asn Ile Ser Asp Leu Lys Pro Gly Val Gln Tyr Asn Ile Asn Pro
      260          265          270
Tyr Leu Leu Gln Ser Asn Lys Thr Lys Gly Asp Pro Leu Gly Thr Glu
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Gly Gly Leu Asp Ala Ser Asn Thr Glu Arg Ser Arg Ala Gly Ser Pro
      290          295          300
Thr Ala Pro Val His Asp Glu Ser Leu Val Gly Pro Val Asp Pro Ser
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Ser Gly Gln Gln Ser Arg Asp Thr Glu Val Leu Leu Val Gly Leu Glu
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Pro Gly Thr Arg Tyr Asn Ala Thr Val Tyr Ser Gln Ala Ala Asn Gly
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Thr Glu Gly Gln Pro Gln Ala Ile Glu Phe Arg Thr Asn Ala Ile Gln
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Val Phe Asp Val Thr Ala Val Asn Ile Ser Ala Thr Ser Leu Thr Leu
370          375          380
Ile Trp Lys Val Ser Asp Asn Glu Ser Ser Ser Asn Tyr Thr Tyr Lys
385          390          395          400
Ile His Val Ala Gly Glu Thr Asp Ser Ser Asn Leu Asn Val Ser Glu
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Pro Arg Ala Val Ile Pro Gly Leu Arg Ser Ser Thr Phe Tyr Asn Ile
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Thr Val Cys Pro Val Leu Gly Asp Ile Glu Gly Thr Pro Gly Phe Leu

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 <212> DNA  
 <213> Homo sapiens

<400> 43

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&lt;210&gt; 44

&lt;211&gt; 1337

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 44

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Ile Leu Cys Ala Gly Gly Thr Pro Ser Pro Ile Pro Asp Pro Ser Val
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Arg Pro Ala Thr Ser Tyr Val Phe Ser Ile Thr Pro Gly Ile Gly Asn
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 Lys Ser Pro Asp Gly Ala Ser Glu Tyr Val Tyr His Leu Val Ile Glu  
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 Ser Lys His Gly Ser Asn His Thr Ser Thr Tyr Asp Lys Ala Ile Thr  
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 Leu Gln Gly Leu Ile Pro Gly Thr Leu Tyr Asn Ile Thr Ile Ser Pro  
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 Glu Val Asp His Val Trp Gly Asp Pro Asn Ser Thr Ala Gln Tyr Thr  
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 Arg Pro Ser Asn Val Ser Asn Ile Asp Val Ser Thr Asn Thr Thr Ala  
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 Ala Thr Leu Ser Trp Gln Asn Phe Asp Asp Ala Ser Pro Thr Tyr Ser  
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Ser	Met	Ala	Ser	Phe	Asp	Cys	Glu	Val	Val	Pro	Lys	Glu	Pro	Ala	Leu
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Glu	Val	Ser	Ser	Gly	Ala	Trp	Asn	Asn	Ala	Thr	His	Leu	Glu	Ser	Cys
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Phe	Ser	Thr	Ser	Tyr	Asn	Ile	Ser	Ile	Thr	Thr	Val	Ser	Cys	Gly	Lys
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<210> 45  
 <211> 122  
 <212> PRT  
 <213> Homo sapiens

<400> 45  
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 Tyr Leu Val Arg Asp Tyr Met Lys Gln Ser Pro Pro Glu Ser Glu Ile  
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<210> 46  
 <211> 4426  
 <212> DNA  
 <213> Mus musculus

&lt;400&gt; 46

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&lt;210&gt; 47

&lt;211&gt; 1238

&lt;212&gt; PRT

&lt;213&gt; Mus musculus

&lt;400&gt; 47

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Val Leu Cys Ala Gly Ala Ala Pro Asn Pro Ile Phe Asp Ile Glu Ala
 35          40          45
Val Val Ser Pro Thr Ser Val Leu Leu Thr Trp Lys His Asn Asp Ser
 50          55          60
Gly Ala Ser Glu Cys Arg Ile Glu Asn Lys Met Glu Ser Asn Leu Thr
 65          70          75          80
Phe Pro Val Lys Asn Gln Thr Ser Cys Asn Ile Thr Gly Leu Ser Pro
 85          90          95
Gly Thr Ser Tyr Thr Phe Ser Ile Ile Ser Val Thr Thr Asn Glu Thr
100          105          110
Leu Asn Lys Thr Ile Thr Thr Glu Pro Trp Pro Val Ser Asp Leu His
115          120          125
Val Thr Ser Val Gly Val Thr Gln Ala Arg Leu Thr Trp Ser Asn Ala
130          135          140
Asn Gly Thr Ala Ser Tyr Arg Met Leu Ile Glu Glu Leu Thr Thr His
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Ser Ser Val Asn Ile Ser Gly Leu Lys Pro Gly Thr Asn Asn Thr Phe
165          170          175
Ala Phe Pro Glu Ser Asn Glu Thr Gln Ala Asp Phe Ala Val Ala Glu
180          185          190
Glu Val Pro Asp Ala Asn Gly Thr Lys Arg Ile Pro Val Thr Asn Leu
195          200          205
Ser Gln Leu His Lys Asn Ser Leu Val Ser Val Asp Pro Pro Ser Gly
210          215          220
Gln Asp Pro Ser Leu Thr Glu Ile Leu Leu Thr Asp Leu Lys Pro Asp
225          230          235          240
Thr Gln Tyr Asn Ala Thr Ile Tyr Ser Gln Ala Ala Asn Gly Thr Glu
245          250          255
Gly Gln Pro Arg Asn Lys Val Phe Lys Thr Asn Ser Thr Gln Val Ser

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Ala	Ile	Ile	Leu	Gly	Leu	Ser	Ser	Ser	Thr	Leu	Tyr	Asn	Ile	Thr	Val			
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His	Pro	Phe	Leu	Gly	Gln	Thr	Glu	Gly	Thr	Pro	Gly	Phe	Leu	Gln	Val			
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Tyr	Thr	Ser	Pro	Asp	Gln	Val	Ser	Asp	Phe	Arg	Val	Thr	Asn	Val	Ser			
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Thr	Arg	Ala	Ile	Gly	Leu	Ala	Trp	Arg	Ser	Asn	Asp	Ser	Lys	Ser	Phe			
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Glu	Ile	Phe	Ile	Lys	Gln	Asp	Gly	Gly	Glu	Lys	His	Arg	Asn	Ala	Ser			
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Tyr	His	Phe	Glu	Ile	Ile	Pro	Arg	Gly	Pro	Asp	Gly	Thr	Glu	Gly	Leu			
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Ser	Ser	Thr	Val	Asn	Gly	Ser	Thr	Asp	Pro	Ser	Ala	Val	Thr	Asp	Ile			
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Arg	Val	Val	Asn	Ile	Ser	Thr	Thr	Glu	Met	Gln	Leu	Glu	Trp	Gln	Asn			
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Thr	Asp	Asp	Ala	Ser	Gly	Tyr	Thr	Tyr	His	Leu	Val	Leu	Glu	Ser	Lys			
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Ser	Gly	Ser	Ile	Ile	Arg	Thr	Asn	Ser	Ser	Gln	Lys	Trp	Ile	Thr	Val			
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Gly	Ser	Leu	Thr	Pro	Gly	Thr	Leu	Tyr	Asn	Val	Thr	Ile	Phe	Pro	Glu			
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Val	Asp	Gln	Ile	Gln	Gly	Ile	Ser	Asn	Ser	Ile	Thr	Gln	Tyr	Thr	Arg			
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Pro	Ser	Ser	Val	Ser	His	Ile	Glu	Val	Asn	Thr	Thr	Thr	Thr	Thr	Ala			
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Thr Asn Gly Tyr Ile Ala						
1235						

&lt;210&gt; 48

&lt;211&gt; 6314

&lt;212&gt; DNA

<213> *Rattus norvegicus*

&lt;400&gt; 48

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&lt;210&gt; 49

&lt;211&gt; 1216

&lt;212&gt; PRT

&lt;213&gt; Rattus norvegicus

&lt;400&gt; 49

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Val Val Cys Thr Gly Ala Ala Pro Ser Pro Val Phe Asp Val Glu Ala
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50     55     60
Ala Thr Ser Glu Tyr Lys Ile Asn Glu Gly Asn Thr Leu Arg Tyr Thr
65     70     75     80
Val Lys Asn Gln Thr Ser Phe Asn Ile Thr Gly Leu Ser Pro Ala Thr
85     90     95
Ser Tyr Lys Phe Ser Ile Thr Leu Gly Thr Val Asn Glu Thr Ser Gly
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Lys Pro Thr Tyr Lys Asn Ile Thr Thr Glu Pro Trp Pro Val Ser Asp
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Thr Glu Gly Val Ser Asp Pro Pro Ser Ala Arg Asp Pro Ser Leu Thr
195    200    205
Glu Val Leu Leu Thr Glu Leu Lys Pro Asp Thr Gln Tyr Lys Val Thr
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Val Phe Lys Thr Asn Pro Ile Gln Val Ser Asp Ile Arg Ala Val Asn
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Ser His Ala Ser Phe Thr Tyr Lys Ile Tyr Val Ala Gly Gly Ser Asp
275    280    285
Ser Ile Asn Glu Thr Val Asn Glu Thr Gln Ala Val Ile Arg Gly Leu
290    295    300
Ser Ser Ser Thr Leu Tyr Asn Ile Thr Val Leu Pro Phe Leu Gly Gln
305    310    315    320
Thr Ala Gly Ile Pro Gly Phe Leu Gln Val Tyr Thr Ser Pro Arg Pro
325    330    335
Val Ser Asp Phe Arg Val Thr Asn Val Ser Leu Arg Glu Ile Gly Leu
340    345    350

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&lt;211&gt; 1785

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 50

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 <211> 594  
 <212> PRT  
 <213> Homo sapiens

<400> 51  
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 Cys Lys Leu Asn Lys Lys Leu Lys Ser Tyr Ser Leu Ser Arg Lys Lys  
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 85 90 95  
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 100 105 110  
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 Asp Cys Leu Gln Gly Ile Arg Lys Gly Leu Gln His Gly Phe Phe Asp  
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&lt;210&gt; 57

&lt;211&gt; 498

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 57

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35          40          45
Tyr Leu Asp Ile Thr Asp Arg Leu Cys Phe Ala Ile Leu Tyr Ser Arg
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Pro Lys Ser Ala Ser Asn Val His Tyr Phe Ser Ile Asp Asn Glu Leu
65          70          75          80
Glu Tyr Glu Asn Phe Tyr Ala Asp Phe Gly Pro Leu Asn Leu Ala Met
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Val Tyr Arg Tyr Cys Cys Lys Ile Asn Lys Lys Leu Lys Ser Ile Thr
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115         120         125
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Gly Arg Thr Pro Glu Glu Ala Tyr Arg Ile Leu Ile Phe Gly Glu Thr
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Ser Tyr Ile Pro Phe Arg Asp Ala Ala Tyr Gly Ser Cys Asn Phe Tyr
165         170         175
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Ile Ala Phe Cys Gly Pro His Ser Arg Ala Arg Leu Glu Ser Gly Tyr

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Leu Arg

&lt;210&gt; 58

&lt;211&gt; 4960

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 58

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<210> 59  
 <211> 471  
 <212> PRT  
 <213> Homo sapiens

<400> 59

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Pro	Lys	Ser	Ala	Ser	Asn	Val	His	Tyr	Phe	Ser	Ile	Asp	Asn	Glu	Leu
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&lt;210&gt; 60

&lt;211&gt; 2646

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; 2300

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 60

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<210> 61  
 <211> 459  
 <212> PRT  
 <213> Homo sapiens

<400> 61

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Ser	Ser	Thr	Gln	Gln	Asp	Pro	Arg	Arg	Arg	Asp	Pro	Gln	Asp	Asp	Val	35	40	45	
Tyr	Leu	Asp	Ile	Thr	Asp	Arg	Leu	Cys	Phe	Ala	Ile	Leu	Tyr	Ser	Arg	50	55	60	
Pro	Lys	Ser	Ala	Ser	Asn	Val	His	Tyr	Phe	Ser	Ile	Asp	Asn	Glu	Leu	65	70	75	80
Glu	Tyr	Glu	Asn	Phe	Tyr	Ala	Asp	Phe	Gly	Pro	Leu	Asn	Leu	Ala	Met	85	90	95	
Val	Tyr	Arg	Tyr	Cys	Cys	Lys	Ile	Asn	Lys	Lys	Leu	Lys	Ser	Ile	Thr	100	105	110	
Met	Leu	Arg	Lys	Lys	Ile	Val	His	Phe	Thr	Gly	Ser	Asp	Gln	Arg	Lys	115	120	125	
Gln	Ala	Asn	Ala	Ala	Phe	Leu	Val	Gly	Cys	Tyr	Met	Val	Ile	Tyr	Leu	130	135	140	
Gly	Arg	Thr	Pro	Glu	Glu	Ala	Tyr	Arg	Ile	Leu	Ile	Phe	Gly	Glu	Thr	145	150	155	160
Ser	Tyr	Ile	Pro	Phe	Arg	Asp	Ala	Ala	Tyr	Gly	Ser	Cys	Asn	Phe	Tyr	165	170	175	
Ile	Thr	Leu	Leu	Asp	Cys	Phe	His	Ala	Val	Lys	Lys	Ala	Met	Gln	Tyr	180	185	190	
Gly	Phe	Leu	Asn	Phe	Asn	Ser	Phe	Asn	Leu	Asp	Glu	Tyr	Glu	His	Tyr	195	200	205	
Glu	Lys	Ala	Glu	Asn	Gly	Asp	Leu	Asn	Trp	Ile	Ile	Pro	Asp	Arg	Phe	210	215	220	
Ile	Ala	Phe	Cys	Gly	Pro	His	Ser	Arg	Ala	Arg	Leu	Glu	Ser	Gly	Tyr	225	230	235	240
His	Gln	His	Ser	Pro	Glu	Thr	Tyr	Ile	Gln	Tyr	Phe	Lys	Asn	His	Asn	245	250	255	

Val Thr Thr Ile Ile Arg Leu Asn Lys Arg Met Tyr Asp Ala Lys Arg  
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 Phe Thr Asp Ala Gly Phe Asp His His Asp Leu Phe Phe Ala Asp Gly  
 275 280 285  
 Ser Thr Pro Thr Asp Ala Ile Val Lys Glu Phe Leu Asp Ile Cys Glu  
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 Asn Ala Glu Gly Ala Ile Ala Val His Cys Lys Ala Gly Leu Gly Arg  
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 Thr Gly Thr Leu Ile Ala Cys Tyr Ile Met Lys His Tyr Arg Met Thr  
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 385 390 395 400  
 Ser Ile Asn Gly Val Glu Asn Gln Asp Gln Glu Pro Glu Pro Tyr  
 405 410 415  
 Ser Asp Asp Asp Glu Ile Asn Gly Val Thr Gln Gly Asp Arg Leu Arg  
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<210> 62  
 <211> 2160  
 <212> DNA  
 <213> Homo sapiens

<400> 62  
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&lt;210&gt; 63

&lt;211&gt; 700

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 63

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 20             25             30
Thr Thr Thr Ser Gly Pro Pro Asp Pro Gly Ala Ser Gln Pro Leu Leu
 35             40             45
Ala Trp Leu Leu Leu Pro Leu Leu Leu Leu Leu Val Leu Leu Leu
 50             55             60
Ala Ala Tyr Phe Phe Arg Phe Arg Lys Gln Arg Lys Ala Val Val Ser
 65             70             75             80
Thr Ser Asp Lys Lys Met Pro Asn Gly Ile Leu Glu Glu Gln Glu Gln
 85             90             95
Gln Arg Val Met Leu Leu Ser Arg Ser Pro Ser Gly Pro Lys Lys Tyr
 100            105            110
Phe Pro Ile Pro Val Glu His Leu Glu Glu Glu Ile Arg Ile Arg Ser
 115            120            125
Ala Asp Asp Cys Lys Gln Phe Arg Glu Glu Phe Asn Ser Leu Pro Ser
 130            135            140
Gly His Ile Gln Gly Thr Phe Glu Leu Ala Asn Lys Glu Glu Asn Arg
 145            150            155            160
Glu Lys Asn Arg Tyr Pro Asn Ile Leu Pro Asn Asp His Ser Arg Val
 165            170            175
Ile Leu Ser Gln Leu Asp Gly Ile Pro Cys Ser Asp Tyr Ile Asn Ala
 180            185            190
Ser Tyr Ile Asp Gly Tyr Lys Glu Lys Asn Lys Phe Ile Ala Ala Gln
 195            200            205
Gly Pro Lys Gln Glu Thr Val Asn Asp Phe Trp Arg Met Val Trp Glu
 210            215            220
Gln Lys Ser Ala Thr Ile Val Met Leu Thr Asn Leu Lys Glu Arg Lys
 225            230            235            240
Glu Glu Lys Cys His Gln Tyr Trp Pro Asp Gln Gly Cys Trp Thr Tyr
 245            250            255
Gly Asn Ile Arg Val Cys Val Glu Asp Cys Val Val Leu Val Asp Tyr
 260            265            270
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 275            280            285
Ala Pro Arg Leu Val Ser Gln Leu His Phe Thr Ser Trp Pro Asp Phe
 290            295            300

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 340 345 350  
 Ala Met Met His Ala Glu Gln Lys Val Asp Val Phe Glu Phe Val Ser  
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 Arg Ile Arg Asn Gln Arg Pro Gln Met Val Gln Thr Asp Met Gln Tyr  
 370 375 380  
 Thr Phe Ile Tyr Gln Ala Leu Leu Glu Tyr Tyr Leu Tyr Gly Asp Thr  
 385 390 395 400  
 Glu Leu Asp Val Ser Ser Leu Glu Lys His Leu Gln Thr Met His Gly  
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 Thr Thr Thr His Phe Asp Lys Ile Gly Leu Glu Glu Glu Phe Arg Lys  
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 Ser Glu Ala Ile Ser Ile Arg Asp Phe Leu Val Thr Leu Asn Gln Pro  
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 580 585 590  
 His Gly Trp Pro Glu Ile Gly Ile Pro Ala Glu Gly Lys Gly Met Ile  
 595 600 605  
 Asp Leu Ile Ala Ala Val Gln Lys Gln Gln Gln Thr Gly Asn His  
 610 615 620  
 Pro Ile Thr Val His Cys Ser Ala Gly Ala Gly Arg Thr Gly Thr Phe  
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 Asp Val Phe Gln Ala Val Lys Ser Leu Arg Leu Gln Arg Pro His Met  
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&lt;210&gt; 64

&lt;211&gt; 2827

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;220&gt;

<221> misc feature  
 <222> 63, 295, 296  
 <223> n = A,T,C or G

<400> 64

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aaaaaa 2827

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<210> 65  
 <211> 699  
 <212> PRT  
 <213> Mus musculus

&lt;400&gt; 65

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          20          25          30
Thr Ser Thr Thr Ala Gly Pro Pro Asp Pro Gly Ala Ser Gln Pro Leu
          35          40          45
Leu Thr Trp Leu Leu Leu Pro Leu Leu Leu Leu Leu Phe Leu Leu Ala
          50          55          60
Ala Tyr Phe Phe Arg Phe Arg Lys Gln Arg Lys Ala Val Val Ser Ser
65          70          75          80
Asn Asp Lys Lys Met Pro Asn Gly Ile Leu Glu Glu Gln Glu Gln Gln
          85          90          95
Arg Val Met Leu Leu Ser Arg Ser Pro Ser Gly Pro Lys Lys Phe Phe
          100          105          110
Pro Ile Pro Val Glu His Leu Glu Glu Glu Ile Arg Val Arg Ser Ala
          115          120          125
Asp Asp Cys Lys Arg Phe Arg Glu Glu Phe Asn Ser Leu Pro Ser Gly
          130          135          140
His Ile Gln Gly Thr Phe Glu Leu Ala Asn Lys Glu Glu Asn Arg Glu
145          150          155          160
Lys Asn Arg Tyr Pro Asn Ile Leu Pro Asn Asp His Cys Arg Val Ile
          165          170          175
Leu Ser Gln Val Asp Gly Ile Pro Cys Ser Asp Tyr Ile Asn Ala Ser
          180          185          190
Tyr Ile Asp Gly Tyr Lys Glu Lys Asn Lys Phe Ile Ala Ala Gln Gly
          195          200          205
Pro Lys Gln Glu Thr Val Asn Asp Phe Trp Arg Met Val Trp Glu Gln
210          215          220
Arg Ser Ala Thr Ile Val Met Leu Thr Asn Leu Lys Glu Arg Lys Glu
225          230          235          240
Glu Lys Cys Tyr Gln Tyr Trp Pro Asp Gln Gly Cys Trp Thr Tyr Gly
          245          250          255
Asn Ile Arg Val Cys Val Glu Asp Cys Val Val Leu Val Asp Tyr Thr
          260          265          270
Ile Arg Lys Phe Cys Ile His Pro Gln Leu Pro Asp Ser Cys Lys Ala
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Pro Arg Leu Val Ser Gln Leu His Phe Thr Ser Trp Pro Asp Phe Gly
          290          295          300
Val Pro Phe Thr Pro Ile Gly Met Leu Lys Phe Leu Lys Lys Val Lys
305          310          315          320
Thr Leu Asn Pro Ser His Ala Gly Pro Ile Val Val His Cys Ser Ala
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          340          345          350
Met Ile His Ser Glu Gln Lys Val Asp Val Phe Glu Phe Val Ser Arg
          355          360          365
Ile Arg Asn Gln Arg Pro Gln Met Val Gln Thr Asp Val Gln Tyr Thr
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Phe Ile Tyr Gln Ala Leu Leu Glu Tyr Tyr Leu Tyr Gly Asp Thr Glu
385          390          395          400
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Thr Asn Val Arg Ile Met Lys Glu Asn Met Arg Thr Gly Asn Leu Pro
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 690 695

&lt;210&gt; 66

&lt;211&gt; 2155

&lt;212&gt; DNA

&lt;213&gt; Rattus norvegicus

&lt;400&gt; 66

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&lt;210&gt; 67

&lt;211&gt; 659

&lt;212&gt; PRT

&lt;213&gt; Rattus norvegicus

&lt;400&gt; 67

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35          40          45
Ile Leu Glu Glu Gln Glu Gln Gln Arg Val Met Leu Leu Ser Arg Ser
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Pro Ser Gly Pro Lys Lys Tyr Phe Pro Ile Pro Val Glu His Leu Glu
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Glu Glu Ile Arg Val Arg Ser Ala Asp Asp Cys Lys Arg Phe Arg Glu
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Pro Asn Asp His Cys Arg Val Ile Leu Ser Gln Leu Asp Gly Ile Pro
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Cys Ser Asp Tyr Ile Asn Ala Ser Tyr Ile Asp Gly Tyr Lys Glu Lys
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Phe Trp Arg Met Val Trp Glu Gln Arg Ser Ala Thr Ile Val Met Leu
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Thr Asn Leu Lys Glu Arg Lys Glu Glu Lys Cys Tyr Gln Tyr Trp Pro
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Phe Thr Ser Trp Pro Asp Phe Gly Val Pro Phe Thr Pro Ile Gly Met

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Gln	Tyr	Trp	Pro	Thr	Glu	Gly	Ser	Val	Thr	His	Gly	Asp	Ile	Thr	Ile	
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Glu	Ile	Lys	Ser	Asp	Thr	Leu	Ser	Glu	Ala	Ile	Ser	Ile	Arg	Asp	Phe	
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Leu	Val	Thr	Phe	Thr	Gln	Pro	Leu	Ala	Arg	Gln	Glu	Glu	Gln	Val	Arg	
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Met	Val	Arg	Gln	Phe	His	Phe	His	Ala	Trp	Pro	Glu	Val	Gly	Ile	Pro	
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Gln	Gln	Gln	Thr	Asp	Asn	His	Pro	Ile	Thr	Val	His	Cys	Ser	Ala	Gly	
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<210> 68
<211> 2938
<212> DNA
<213> Homo sapiens
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&lt;400&gt; 68

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&lt;210&gt; 69

&lt;211&gt; 780

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 69

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Met Arg Leu Arg Arg Leu Ser Thr Lys Tyr Arg Thr Glu Lys Ile Tyr			
35	40	45	
Pro Thr Ala Thr Gly Glu Lys Glu Glu Asn Val Lys Lys Asn Arg Tyr			
50	55	60	
Lys Asp Ile Leu Pro Phe Asp His Ser Arg Val Lys Leu Thr Leu Lys			
65	70	75	80
Thr Pro Ser Gln Asp Ser Asp Tyr Ile Asn Ala Asn Phe Ile Lys Gly			
85	90	95	
Val Tyr Gly Pro Lys Ala Tyr Val Ala Thr Gln Gly Pro Leu Ala Asn			
100	105	110	
Thr Val Ile Asp Phe Trp Arg Met Val Trp Glu Tyr Asn Val Val Ile			
115	120	125	
Ile Val Met Ala Cys Arg Glu Phe Glu Met Gly Arg Lys Lys Cys Glu			
130	135	140	
Arg Tyr Trp Pro Leu Tyr Gly Glu Asp Pro Ile Thr Phe Ala Pro Phe			
145	150	155	160
Lys Ile Ser Cys Glu Asp Glu Gln Ala Arg Thr Asp Tyr Phe Ile Arg			
165	170	175	
Thr Leu Leu Leu Glu Phe Gln Asn Glu Ser Arg Arg Leu Tyr Gln Phe			
180	185	190	
His Tyr Val Asn Trp Pro Asp His Asp Val Pro Ser Ser Phe Asp Ser			
195	200	205	
Ile Leu Asp Met Ile Ser Leu Met Arg Lys Tyr Gln Glu His Glu Asp			
210	215	220	
Val Pro Ile Cys Ile His Cys Ser Ala Gly Cys Gly Arg Thr Gly Ala			
225	230	235	240
Ile Cys Ala Ile Asp Tyr Thr Trp Asn Leu Lys Ala Gly Lys Ile			
245	250	255	
Pro Glu Glu Phe Asn Val Phe Asn Leu Ile Gln Glu Met Arg Thr Gln			
260	265	270	
Arg His Ser Ala Val Gln Thr Lys Glu Gln Tyr Glu Leu Val His Arg			
275	280	285	
Ala Ile Ala Gln Leu Phe Glu Lys Gln Leu Gln Leu Tyr Glu Ile His			
290	295	300	
Gly Ala Gln Lys Ile Ala Asp Gly Val Asn Glu Ile Asn Thr Glu Asn			
305	310	315	320
Met Val Ser Ser Ile Glu Pro Glu Lys Gln Asp Ser Pro Pro Pro Lys			
325	330	335	
Pro Pro Arg Thr Arg Ser Cys Leu Val Glu Gly Asp Ala Lys Glu Glu			
340	345	350	
Ile Leu Gln Pro Pro Glu Pro His Pro Val Pro Pro Ile Leu Thr Pro			
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Ser Pro Pro Ser Ala Phe Pro Thr Val Thr Thr Val Trp Gln Asp Asn			
370	375	380	
Asp Arg Tyr His Pro Lys Pro Val Leu His Met Val Ser Ser Glu Gln			
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His Ser Ala Asp Leu Asn Arg Asn Tyr Ser Lys Ser Thr Glu Leu Pro			
405	410	415	
Gly Lys Asn Glu Ser Thr Ile Glu Gln Ile Asp Lys Lys Leu Glu Arg			
420	425	430	
Asn Leu Ser Phe Glu Ile Lys Lys Val Pro Leu Gln Glu Gly Pro Lys			
435	440	445	
Ser Phe Asp Gly Asn Thr Leu Leu Asn Arg Gly His Ala Ile Lys Ile			
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Lys Ser Ala Ser Pro Cys Ile Ala Asp Lys Ile Ser Lys Pro Gln Glu			

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Glu	Thr	Pro	Asp	Leu	Val	Asp	His	Asp	Asn	Thr	Ser	Pro	Leu	Phe	Arg
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Thr	Pro	Leu	Ser	Phe	Thr	Asn	Pro	Leu	His	Ser	Asp	Asp	Ser	Asp	Ser
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Gln	Glu	Arg	Ser	Glu	Gln	Lys	Lys	Ser	Glu	Gly	Leu	Ile	Thr	Ser	Glu
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gggactaaca gcagtgtaga ttgttacctt aatatttttt gctgggacca tctacctgcc 2520
ttatactaca cttaggaaaa agtattacat atggtttatt ttgaaacttc aagtattatt 2580
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tttatgatat attgagttta aggactactc tttttctggt ttatcatgta tgcattattt 2700
tgtatatgta cagggcaagt aggtatataa tttgataaag ttgcaattga aatattatta 2760
acagaagatg taagaaatth ctgcatggtc taaatctttg tgtactttat ttgtaaatta 2820
tttgccctgg agtttttaga aatagtttct gaattttaaa cttgctggat tcatgcagcc 2880
agctttgcag gttatcagag atcaaagatt gtaataataa ttttgtaa atgtgaagcaa 2940
aagttatttt tatattatat acagtcta atgttcacct aattgttcct gttttcatct 3000
agtcagagat tcagtaagtg ccttggaaca atattgaatt ctcttagctt gtgtgtgttt 3060
ctttaatatt tgaactcaag tgggattaga agactatcaa aatacatgta tgtttcagat 3120
atttgacctg tcattaaaaa aaacaaacag ttttacagt 3160

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&lt;210&gt; 71

&lt;211&gt; 780

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 71

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Met Glu Gln Val Glu Ile Leu Arg Lys Phe Ile Gln Arg Val Gln Ala
 1           5           10          15
Met Lys Ser Pro Asp His Asn Gly Glu Asp Asn Phe Ala Arg Asp Phe
 20          25          30
Met Arg Leu Arg Arg Leu Ser Thr Lys Tyr Arg Thr Glu Lys Ile Tyr
 35          40          45
Pro Thr Ala Thr Gly Glu Lys Glu Glu Asn Val Lys Lys Asn Arg Tyr
 50          55          60
Lys Asp Ile Leu Pro Phe Asp His Ser Arg Val Lys Leu Thr Leu Lys

```

65					70					75					80
Thr	Pro	Ser	Gln	Asp	Ser	Asp	Tyr	Ile	Asn	Ala	Asn	Phe	Ile	Lys	Gly
				85					90					95	
Val	Tyr	Gly	Pro	Lys	Ala	Tyr	Val	Ala	Thr	Gln	Gly	Pro	Leu	Ala	Asn
			100					105					110		
Thr	Val	Ile	Asp	Phe	Trp	Arg	Met	Ile	Trp	Glu	Tyr	Asn	Val	Val	Ile
		115					120					125			
Ile	Val	Met	Ala	Cys	Arg	Glu	Phe	Glu	Met	Gly	Arg	Lys	Lys	Cys	Glu
	130					135				140					
Arg	Tyr	Trp	Pro	Leu	Tyr	Gly	Glu	Asp	Pro	Ile	Thr	Phe	Ala	Pro	Phe
145					150				155						160
Lys	Ile	Ser	Cys	Glu	Asp	Glu	Gln	Ala	Arg	Thr	Asp	Tyr	Phe	Ile	Arg
			165						170					175	
Thr	Leu	Leu	Leu	Glu	Phe	Gln	Asn	Glu	Ser	Arg	Arg	Leu	Tyr	Gln	Phe
		180						185					190		
His	Tyr	Val	Asn	Trp	Pro	Asp	His	Asp	Val	Pro	Ser	Ser	Phe	Asp	Ser
	195					200					205				
Ile	Leu	Asp	Met	Ile	Ser	Leu	Met	Arg	Lys	Tyr	Gln	Glu	His	Glu	Asp
	210					215				220					
Val	Pro	Ile	Cys	Ile	His	Cys	Ser	Ala	Gly	Cys	Gly	Arg	Thr	Gly	Ala
225					230				235						240
Ile	Cys	Ala	Ile	Asp	Tyr	Thr	Trp	Asn	Leu	Leu	Lys	Ala	Gly	Lys	Ile
			245					250						255	
Pro	Glu	Glu	Phe	Asn	Val	Phe	Asn	Leu	Ile	Gln	Glu	Met	Arg	Thr	Gln
			260				265						270		
Arg	His	Ser	Ala	Val	Gln	Thr	Lys	Glu	Gln	Tyr	Glu	Leu	Val	His	Arg
	275					280						285			
Ala	Ile	Ala	Gln	Leu	Phe	Glu	Lys	Gln	Leu	Gln	Leu	Tyr	Glu	Ile	His
	290				295					300					
Gly	Ala	Gln	Lys	Ile	Ala	Asp	Gly	Val	Asn	Glu	Ile	Asn	Thr	Glu	Asn
305				310					315						320
Met	Ile	Ser	Ser	Ile	Glu	Pro	Glu	Lys	Gln	Asp	Ser	Pro	Pro	Pro	Lys
			325						330					335	
Pro	Pro	Arg	Thr	Arg	Ser	Cys	Leu	Val	Glu	Gly	Asp	Ala	Lys	Glu	Glu
		340					345					350			
Ile	Leu	Gln	Pro	Pro	Glu	Pro	His	Pro	Val	Pro	Pro	Ile	Leu	Thr	Pro
	355					360						365			
Ser	Pro	Pro	Ser	Ala	Phe	Pro	Thr	Val	Thr	Thr	Val	Trp	Gln	Asp	Asn
	370				375						380				
Asp	Arg	Tyr	His	Pro	Lys	Pro	Val	Leu	His	Met	Val	Ser	Ser	Glu	Gln
385				390					395					400	
His	Ser	Ala	Asp	Leu	Asn	Arg	Asn	Tyr	Ser	Lys	Ser	Thr	Glu	Leu	Pro
			405				410						415		
Gly	Lys	Asn	Glu	Ser	Thr	Ile	Glu	Gln	Ile	Asp	Lys	Lys	Leu	Glu	Arg
		420					425						430		
Asn	Leu	Ser	Phe	Glu	Ile	Lys	Lys	Val	Pro	Leu	Gln	Glu	Gly	Pro	Lys
	435					440					445				
Ser	Phe	Asp	Gly	Asn	Thr	Leu	Leu	Asn	Arg	Gly	His	Ala	Ile	Lys	Ile
	450				455						460				
Lys	Ser	Ala	Ser	Pro	Cys	Ile	Ala	Asp	Lys	Ile	Ser	Lys	Pro	Gln	Glu
465				470					475					480	
Leu	Ser	Ser	Asp	Leu	Asn	Val	Gly	Asp	Thr	Ser	Gln	Asn	Ser	Cys	Val
			485					490						495	
Asp	Cys	Ser	Val	Thr	Gln	Ser	Asn	Lys	Val	Ser	Val	Thr	Pro	Pro	Glu
	500						505					510			
Glu	Ser	Gln	Asn	Ser	Asp	Thr	Pro	Pro	Arg	Pro	Asp	Arg	Leu	Pro	Leu
	515					520					525				
Asp	Glu	Lys	Gly	His	Val	Thr	Trp	Ser	Phe	His	Gly	Pro	Glu	Asn	Ala

530		535		540
Ile Pro Ile Pro Asp	Leu Ser Glu Gly Asn Ser	Ser Asp Ile Asn Tyr		
545	550	555	560	
Gln Thr Arg Lys Thr	Val Ser Leu Thr Pro Ser	Pro Thr Thr Gln Val		
	565	570	575	
Glu Thr Pro Asp Leu	Val Asp His Asp Asn Thr Ser	Pro Leu Phe Arg		
	580	585	590	
Thr Pro Leu Ser Phe	Thr Asn Pro Leu His Ser Asp	Asp Ser Asp Ser		
	595	600	605	
Asp Glu Arg Asn Ser	Asp Gly Ala Val Thr Gln Asn Lys	Thr Asn Ile		
	610	615	620	
Ser Thr Ala Ser Ala	Thr Val Ser Ala Ala Thr Ser	Thr Glu Ser Ile		
625	630	635	640	
Ser Thr Arg Lys Val	Leu Pro Met Ser Ile Ala Arg	His Asn Ile Ala		
	645	650	655	
Gly Thr Thr His Ser	Gly Ala Glu Lys Asp Val Asp	Val Ser Glu Asp		
	660	665	670	
Ser Pro Pro Pro Leu	Pro Glu Arg Thr Pro Glu Ser	Phe Val Leu Ala		
	675	680	685	
Ser Glu His Asn Thr	Pro Val Arg Ser Glu Trp Ser	Glu Leu Gln Ser		
	690	695	700	
Gln Glu Arg Ser Glu	Gln Lys Lys Ser Glu Gly Leu	Ile Thr Ser Glu		
705	710	715	720	
Asn Glu Lys Cys Asp	His Pro Ala Gly Gly Ile His	Tyr Glu Met Cys		
	725	730	735	
Ile Glu Cys Pro Pro	Thr Phe Ser Asp Lys Arg Glu	Gln Ile Ser Glu		
	740	745	750	
Asn Pro Thr Glu Ala	Thr Asp Ile Gly Phe Gly Asn	Arg Cys Gly Lys		
	755	760	765	
Pro Lys Gly Pro Arg	Asp Pro Pro Ser Glu Trp Thr			
770	775	780		

<210> 72  
 <211> 236  
 <212> DNA  
 <213> Homo sapiens

<400> 72  
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 ttaaagactc cttcacaaga ttcagactat atcaatgcaa attttataaa gggcgtctat 120  
 gggccaaaag catatgtagc aactcaagga ccttttagcaa atacagtaat agatttttgg 180  
 aggatggtat gggagtataa tgttgtgatc attgtaatgg cctgccgaga atttga 236

<210> 73  
 <211> 78  
 <212> PRT  
 <213> Homo sapiens

<400> 73  
 Val Lys Arg Asn Arg Tyr Lys Asp Ile Leu Pro Phe Asp His Ser Arg  
 1 5 10 15  
 Val Lys Leu Thr Leu Lys Thr Pro Ser Gln Asp Ser Asp Tyr Ile Asn  
 20 25 30  
 Ala Asn Phe Ile Lys Gly Val Tyr Gly Pro Lys Ala Tyr Val Ala Thr  
 35 40 45  
 Gln Gly Pro Leu Ala Asn Thr Val Ile Asp Phe Trp Arg Met Val Trp  
 50 55 60

Glu Tyr Asn Val Val Ile Ile Val Met Ala Cys Arg Glu Phe  
65 70 75

<210> 74  
<211> 2676  
<212> DNA  
<213> Mus musculus

<400> 74  
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tgggggcggc acgagttgga cttccagatc ttgaactcct ttggaggctc ctccggcgct 120  
ttcaccacat gccgctccca gtcgatctgc ttgttcgcct cgtagtaggg gaaagcgacg 180  
ctgctcttta agttgcgcgg ggagcccgcc cgggtgcgcgc gcagccgcag ccgcctgcgc 240  
ggcggggagg gagggcgggc cggagcgagc tggggaagac ggagcgggcg ctgcggcgcg 300  
cgggcgggcg gcggggggga cgcgggagga tggagcaagt ggagatcctg aggaggttca 360  
tccagagggg ccaggccatg aagagtccgg atcacaatgg ggaggacaac ttcgcccggg 420  
acttcatgca attgagaaga ttgtctacca aatatagaac agaaaagatt tatcccacag 480  
ccactggaga aaaagaagaa aatgttaaaa agaacagata taaggacata ctgccatttg 540  
atcacagccg agttaagttg actttgaaga ctccatccca agattcagat tatatcaatg 600  
caaattttat taagggtgtg tatgggccaa aagcatatgt ggcaacccaa gggcctttcc 660  
ggaatacagt catagacttc tggaggatga tatgggagta taatgttgtg atgatcgtga 720  
tggcctgtcg agaatttgag atgggaagga aaaagtgtga gcgctactgg cctttgtatg 780  
gagaagatcc tataacattt gcaccattta aaatttcttg tgaatatgaa caagcaagaa 840  
ccgactactt catccgaaca cttttacttg aatttcaaaa tgaatcccg cggctctatc 900  
agtttcatta cgtgaactgg ccagaccatg atgttccttc gtcatttgat tctattctgg 960  
acatgataag cttaatgagg aaataccaag aacatgaaga tgtgcctatt tgtattcatt 1020  
gcagtgcagg ctgtggacga acaggtgcta tttgtgccat agattacacg tggaaacttac 1080  
tgaaagcagg gaaaattcca gaggaattta atgtatttaa ttaatacaa gaaatgagaa 1140  
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cagacttccc aaccgttacc actgtgtggc aggacagtga caggtaccac ccaaagccag 1500  
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aaggcttgac aacctctgga aatgaaaaac atgatgcagg gggcatccac acagaggtt 2520  
ctgcagactc tccacctgct ttcagtgaac agaaagatca aataacaaaa agtccagcag 2580  
aagtcacaga tattggtttt ggtaatcgct gtggaaaacc taaaggacca agagagccac 2640  
cttcagaatg gacatgatgc agggagtgaagg gaga 2676

<210> 75  
<211> 775

&lt;212&gt; PRT

&lt;213&gt; Mus musculus

&lt;400&gt; 75

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Met Glu Gln Val Glu Ile Leu Arg Arg Phe Ile Gln Arg Val Gln Ala
 1           5           10           15
Met Lys Ser Pro Asp His Asn Gly Glu Asp Asn Phe Ala Arg Asp Phe
          20           25           30
Met Arg Leu Arg Arg Leu Ser Thr Lys Tyr Arg Thr Glu Lys Ile Tyr
          35           40           45
Pro Thr Ala Thr Gly Glu Lys Glu Glu Asn Val Lys Lys Asn Arg Tyr
          50           55           60
Lys Asp Ile Leu Pro Phe Asp His Ser Arg Val Lys Leu Thr Leu Lys
65           70           75           80
Thr Pro Ser Gln Asp Ser Asp Tyr Ile Asn Ala Asn Phe Ile Lys Gly
          85           90           95
Val Tyr Gly Pro Lys Ala Tyr Val Ala Thr Gln Gly Pro Phe Arg Asn
          100          105          110
Thr Val Ile Asp Phe Trp Arg Met Ile Trp Glu Tyr Asn Val Val Met
          115          120          125
Ile Val Met Ala Cys Arg Glu Phe Glu Met Gly Arg Lys Lys Cys Glu
          130          135          140
Arg Tyr Trp Pro Leu Tyr Gly Glu Asp Pro Ile Thr Phe Ala Pro Phe
145          150          155          160
Lys Ile Ser Cys Glu Asn Glu Gln Ala Arg Thr Asp Tyr Phe Ile Arg
          165          170          175
Thr Leu Leu Leu Glu Phe Gln Asn Glu Ser Arg Arg Leu Tyr Gln Phe
          180          185          190
His Tyr Val Asn Trp Pro Asp His Asp Val Pro Ser Ser Phe Asp Ser
          195          200          205
Ile Leu Asp Met Ile Ser Leu Met Arg Lys Tyr Gln Glu His Glu Asp
          210          215          220
Val Pro Ile Cys Ile His Cys Ser Ala Gly Cys Gly Arg Thr Gly Ala
225          230          235          240
Ile Cys Ala Ile Asp Tyr Thr Trp Asn Leu Leu Lys Ala Gly Lys Ile
          245          250          255
Pro Glu Glu Phe Asn Val Phe Asn Leu Ile Gln Glu Met Arg Thr Gln
          260          265          270
Arg His Ser Ala Val Gln Thr Lys Glu Gln Tyr Glu Leu Val His Arg
          275          280          285
Ala Ile Ala Gln Leu Phe Glu Lys Gln Leu Gln Leu Tyr Glu Ile His
          290          295          300
Gly Ala Gln Lys Ile Arg Asp Gly Asn Glu Ile Thr Thr Gly Thr Met
305          310          315          320
Val Ser Ser Ile Asp Ser Glu Lys Gln Asp Ser Pro Pro Pro Lys Pro
          325          330          335
Pro Arg Thr Arg Ser Cys Leu Val Glu Gly Asp Ala Lys Glu Glu Ile
          340          345          350
Leu Gln Pro Pro Glu Pro His Pro Val Pro Pro Ile Leu Thr Pro Ser
          355          360          365
Pro Pro Ser Ala Phe Pro Thr Val Thr Thr Val Trp Gln Asp Ser Asp
          370          375          380
Arg Tyr His Pro Lys Pro Val Leu His Met Ala Ser Pro Glu Gln His
385          390          395          400
Pro Ala Asp Leu Asn Arg Ser Tyr Asp Lys Ser Ala Asp Gln Trp Gly
          405          410          415
Lys Ser Glu Ser Ala Ile Glu His Ile Asp Lys Lys Leu Glu Arg Asn
          420          425          430

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Leu Ser Phe Glu Ile Lys Lys Val Pro Leu Gln Glu Gly Pro Lys Ser  
 435 440 445  
 Phe Asp Gly Asn Thr Leu Leu Asn Arg Gly His Ala Ile Lys Ile Lys  
 450 455 460  
 Ser Ala Ser Ser Ser Val Val Asp Arg Thr Ser Lys Pro Gln Glu Leu  
 465 470 475 480  
 Ser Ala Gly Ala Leu Lys Val Asp Asp Val Ser Gln Asn Ser Cys Ala  
 485 490 495  
 Asp Cys Ser Ala Ala His Ser His Arg Ala Ala Glu Ser Ser Glu Glu  
 500 505 510  
 Ser Gln Ser Asn Ser His Thr Pro Pro Arg Pro Asp Cys Leu Pro Leu  
 515 520 525  
 Asp Lys Lys Gly His Val Thr Trp Ser Leu His Gly Pro Glu Asn Ala  
 530 535 540  
 Thr Pro Val Pro Asp Ser Pro Asp Gly Lys Ser Pro Asp Asn His Ser  
 545 550 555 560  
 Gln Thr Leu Lys Thr Val Ser Ser Thr Pro Asn Ser Thr Ala Glu Glu  
 565 570 575  
 Glu Ala His Asp Leu Thr Glu His His Asn Ser Ser Pro Leu Leu Lys  
 580 585 590  
 Ala Pro Leu Ser Phe Thr Asn Pro Leu His Ser Asp Asp Trp His Ser  
 595 600 605  
 Asp Gly Gly Ser Ser Asp Gly Ala Val Thr Arg Asn Lys Thr Ser Ile  
 610 615 620  
 Ser Thr Ala Ser Ala Thr Val Ser Pro Ala Ser Ser Ala Glu Ser Ala  
 625 630 635 640  
 Cys His Arg Arg Val Leu Pro Met Ser Ile Ala Arg Gln Glu Val Ala  
 645 650 655  
 Gly Thr Pro His Ser Gly Ala Glu Lys Asp Ala Asp Val Ser Glu Glu  
 660 665 670  
 Ser Pro Pro Pro Leu Pro Glu Arg Thr Pro Glu Ser Phe Val Leu Ala  
 675 680 685  
 Asp Met Pro Val Arg Pro Glu Trp His Glu Leu Pro Asn Gln Glu Trp  
 690 695 700  
 Ser Glu Gln Arg Glu Ser Glu Gly Leu Thr Thr Ser Gly Asn Glu Lys  
 705 710 715 720  
 His Asp Ala Gly Gly Ile His Thr Glu Ala Ser Ala Asp Ser Pro Pro  
 725 730 735  
 Ala Phe Ser Asp Lys Lys Asp Gln Ile Thr Lys Ser Pro Ala Glu Val  
 740 745 750  
 Thr Asp Ile Gly Phe Gly Asn Arg Cys Gly Lys Pro Lys Gly Pro Arg  
 755 760 765  
 Glu Pro Pro Ser Glu Trp Thr  
 770 775

&lt;210&gt; 76

&lt;211&gt; 1608

&lt;212&gt; DNA

&lt;213&gt; Rattus norvegicus

&lt;400&gt; 76

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 gtgctcggag cgagctgggg aagacggagc gggcgctgcg gcgcgcgggc gggcggcggg 120  
 ggggacgcgg gaggatggag caagtggaga ttctgaggag gttcatccag aggggtccagg 180  
 ccatgaaaag tccggaccac aatggggagg acaacttcgc ccgggacttc atgcgattga 240  
 gaagattgtc taccaaatat agaacagaaa agatttatcc cacagccact ggagaaaaag 300  
 aagaaaatgt taaaaagaac agatataagg acatactgcc atttgatcac agccgagtta 360



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agttgacttt gaagacacca tcccaagatt cagattatat caatgcaaat tttattaagg 420
gtgtatatgg gccgagagca tacgtggcaa cccaagggcc tttggcgaat acagtcatag 480
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catttgcacc atttaaaatt tcttgtgaaa atgaacaagc aagaacagac tacttcattc 660
gaacactttt acttgaattt caaaatgaat cccgtcgact ctatcagttt cattacgtga 720
actggccaga ccatgatgtc ccttcgtcat tcgattctat cctggacatg ataagtctaa 780
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cagtacaaac gaaggagcag tatgaactcg tccatagagc tattgcccac ctgtttgaaa 1020
aacagctaca actgtatgaa atccacggag cccagaaaat cactgatggg aatgaaatta 1080
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ccacaggagt taagttcagg tgatctaaag gttcacgatg tgtctcag 1608

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&lt;210&gt; 77

&lt;211&gt; 382

&lt;212&gt; PRT

&lt;213&gt; Rattus norvegicus

&lt;400&gt; 77

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Met Glu Gln Val Glu Ile Leu Arg Arg Phe Ile Gln Arg Val Gln Ala
 1             5             10             15
Met Lys Ser Pro Asp His Asn Gly Glu Asp Asn Phe Ala Arg Asp Phe
      20             25             30
Met Arg Leu Arg Arg Leu Ser Thr Lys Tyr Arg Thr Glu Lys Ile Tyr
      35             40             45
Pro Thr Ala Thr Gly Glu Lys Glu Glu Asn Val Lys Lys Asn Arg Tyr
      50             55             60
Lys Asp Ile Leu Pro Phe Asp His Ser Arg Val Lys Leu Thr Leu Lys
      65             70             75             80
Thr Pro Ser Gln Asp Ser Asp Tyr Ile Asn Ala Asn Phe Ile Lys Gly
      85             90             95
Val Tyr Gly Pro Arg Ala Tyr Val Ala Thr Gln Gly Pro Leu Ala Asn
      100            105            110
Thr Val Ile Asp Phe Trp Arg Met Ile Trp Glu Tyr Asn Val Val Ile
      115            120            125
Ile Val Met Ala Cys Arg Glu Phe Glu Met Gly Arg Lys Lys Cys Glu
      130            135            140
Arg Tyr Trp Pro Leu Tyr Gly Glu Asp Pro Ile Thr Phe Ala Pro Phe
      145            150            155            160
Lys Ile Ser Cys Glu Asn Glu Gln Ala Arg Thr Asp Tyr Phe Ile Arg
      165            170            175
Thr Leu Leu Leu Glu Phe Gln Asn Glu Ser Arg Arg Leu Tyr Gln Phe
      180            185            190
His Tyr Val Asn Trp Pro Asp His Asp Val Pro Ser Ser Phe Asp Ser
      195            200            205
Ile Leu Asp Met Ile Ser Leu Met Arg Lys Tyr Gln Glu His Glu Asp
      210            215            220
Val Pro Ile Cys Ile His Cys Ser Ala Gly Cys Gly Arg Thr Gly Ala
      225            230            235            240

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Ile	Cys	Ala	Ile	Asp	Tyr	Thr	Trp	Asn	Leu	Leu	Lys	Ala	Gly	Lys	Ile
				245					250					255	
Pro	Glu	Glu	Phe	Asn	Val	Phe	Asn	Leu	Ile	Gln	Glu	Met	Arg	Thr	Gln
			260					265					270		
Arg	His	Ser	Ala	Val	Gln	Thr	Lys	Glu	Gln	Tyr	Glu	Leu	Val	His	Arg
		275					280					285			
Ala	Ile	Ala	Gln	Leu	Phe	Glu	Lys	Gln	Leu	Gln	Leu	Tyr	Glu	Ile	His
		290				295					300				
Gly	Ala	Gln	Lys	Ile	Thr	Asp	Gly	Asn	Glu	Ile	Ser	Thr	Gly	Asn	Met
305					310				315					320	
Val	Ser	Ser	Ile	Asp	Ser	Glu	Lys	Gln	Asp	Ser	Pro	Pro	Pro	Lys	Pro
			325					330						335	
Pro	Arg	Thr	Arg	Ser	Cys	Leu	Val	Glu	Gly	Asp	Ala	Lys	Glu	Glu	Ile
		340						345					350		
Leu	Gln	Pro	Pro	Glu	Pro	His	Pro	Val	Pro	Pro	Ile	Leu	Thr	Pro	Ser
		355				360						365			
Pro	Pro	Ser	Ala	Phe	Pro	Thr	Leu	His	Cys	Val	Ala	Arg	Gln		
		370				375						380			

&lt;210&gt; 78

&lt;211&gt; 4315

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 78

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&lt;210&gt; 79

&lt;211&gt; 1304

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 79

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Leu Thr Thr Ala Lys Met Pro Ser Val Pro Leu Ser Ser Asp Pro Leu
          35          40          45
Pro Thr His Thr Thr Ala Phe Ser Pro Ala Ser Thr Phe Glu Arg Glu
          50          55          60
Asn Asp Phe Ser Glu Thr Thr Thr Ser Leu Ser Pro Asp Asn Thr Ser
          65          70          75          80
Thr Gln Val Ser Pro Asp Ser Leu Asp Asn Ala Ser Ala Phe Asn Thr

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Ser	Gln	Thr	Pro	Ser	Ala	Gly	Thr	Asp	Thr	Gln	Thr	Phe	Ser	Gly	Ser		
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Ala	Ala	Asn	Ala	Lys	Leu	Asn	Pro	Thr	Pro	Gly	Ser	Asn	Ala	Ile	Ser		
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Asp	Val	Pro	Gly	Glu	Arg	Ser	Thr	Ala	Ser	Thr	Phe	Pro	Thr	Asp	Pro		
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Val	Ser	Pro	Leu	Thr	Thr	Thr	Leu	Ser	Leu	Ala	His	His	Ser	Ser	Ala		
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Ala	Leu	Pro	Ala	Arg	Thr	Ser	Asn	Thr	Thr	Ile	Thr	Ala	Asn	Thr	Ser		
			180					185					190				
Asp	Ala	Tyr	Leu	Asn	Ala	Ser	Glu	Thr	Thr	Thr	Leu	Ser	Pro	Ser	Gly		
			195				200					205					
Ser	Ala	Val	Ile	Ser	Thr	Thr	Thr	Ile	Ala	Thr	Thr	Pro	Ser	Lys	Pro		
			210			215					220						
Thr	Cys	Asp	Glu	Lys	Tyr	Ala	Asn	Ile	Thr	Val	Asp	Tyr	Leu	Tyr	Asn		
225					230					235					240		
Lys	Glu	Thr	Lys	Leu	Phe	Thr	Ala	Lys	Leu	Asn	Val	Asn	Glu	Asn	Val		
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Glu	Cys	Gly	Asn	Asn	Thr	Cys	Thr	Asn	Asn	Glu	Val	His	Asn	Leu	Thr		
			260					265					270				
Glu	Cys	Lys	Asn	Ala	Ser	Val	Ser	Ile	Ser	His	Asn	Ser	Cys	Thr	Ala		
			275				280					285					
Pro	Asp	Lys	Thr	Leu	Ile	Leu	Asp	Val	Pro	Pro	Gly	Val	Glu	Lys	Phe		
			290			295					300						
Gln	Leu	His	Asp	Cys	Thr	Gln	Val	Glu	Lys	Ala	Asp	Thr	Thr	Ile	Cys		
305					310					315					320		
Leu	Lys	Trp	Lys	Asn	Ile	Glu	Thr	Phe	Thr	Cys	Asp	Thr	Gln	Asn	Ile		
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Thr	Tyr	Arg	Phe	Gln	Cys	Gly	Asn	Met	Ile	Phe	Asp	Asn	Lys	Glu	Ile		
			340					345					350				
Lys	Leu	Glu	Asn	Leu	Glu	Pro	Glu	His	Glu	Tyr	Lys	Cys	Asp	Ser	Glu		
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Ile	Leu	Tyr	Asn	Asn	His	Lys	Phe	Thr	Asn	Ala	Ser	Lys	Ile	Ile	Lys		
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Thr	Asp	Phe	Gly	Ser	Pro	Gly	Glu	Pro	Gln	Ile	Phe	Cys	Arg	Ser			
385					390					395				400			
Glu	Ala	Ala	His	Gln	Gly	Val	Ile	Thr	Trp	Asn	Pro	Pro	Gln	Arg	Ser		
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 Gly Glu Pro Phe Ile Leu His His Ser Thr Ser Tyr Asn Ser Lys Ala  
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 Leu Val Val Leu Tyr Lys Ile Tyr Asp Leu His Lys Lys Arg Ser Cys  
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 Asn Leu Asp Glu Gln Gln Glu Leu Val Glu Arg Asp Asp Glu Lys Gln  
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 Leu Met Asn Val Glu Pro Ile His Ala Asp Ile Leu Leu Glu Thr Tyr  
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 Lys Arg Lys Ile Ala Asp Glu Gly Arg Pro Phe Leu Ala Glu Phe Gln  
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 Ser Ile Pro Arg Val Phe Ser Lys Phe Pro Ile Lys Glu Ala Arg Lys  
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 Pro Phe Asn Gln Asn Lys Asn Arg Tyr Val Asp Ile Leu Pro Tyr Asp  
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 Tyr Asn Arg Val Glu Leu Ser Glu Ile Asn Gly Asp Ala Gly Ser Asn  
 690                                   695                      700  
 Tyr Ile Asn Ala Ser Tyr Ile Asp Gly Phe Lys Glu Pro Arg Lys Tyr  
 705                                   710                      715                      720  
 Ile Ala Ala Gln Gly Pro Arg Asp Glu Thr Val Asp Asp Phe Trp Arg  
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 Met Ile Trp Glu Gln Lys Ala Thr Val Ile Val Met Val Thr Arg Cys  
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 Lys Glu Lys Ala Thr Gly Arg Glu Val Thr His Ile Gln Phe Thr Ser  
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 835                                   840                      845  
 Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Tyr Ile Gly Ile  
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 865                                   870                      875                      880  
 Gly Tyr Val Val Lys Leu Arg Arg Gln Arg Cys Leu Met Val Gln Val  
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 Glu Phe Gln Arg Leu Pro Ser Tyr Arg Ser Trp Arg Thr Gln His Ile  
 945                                   950                      955                      960  
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 Ser Pro Ala Leu Asn Gln Gly Ser  
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&lt;210&gt; 80

&lt;211&gt; 4597

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 80

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 <212> PRT  
 <213> Homo sapiens

<400> 81

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Lys	Trp	Lys	Asn	Ile	Glu	Thr	Phe	Thr	Cys	Asp	Thr	Gln	Asn	Ile	Thr
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Arg	Cys	Pro	Asp	Tyr	Ile	Ile	Gln	Lys	Leu	Asn	Ile	Val	Asn	Lys	Lys				
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Pro	Asp	His	Gly	Val	Pro	Glu	Asp	Pro	His	Leu	Leu	Leu	Lys	Leu	Arg				
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Arg	Arg	Val	Asn	Ala	Phe	Ser	Asn	Phe	Phe	Ser	Gly	Pro	Ile	Val	Val				
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Lys Pro	Glu Val Met Ile Ala Ala	Gln Gly Pro Leu Lys	Glu Thr Ile		
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Gly Asp	Phe Trp Gln Met Ile Phe	Gln Arg Lys Val Lys	Val Ile Val		
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Met Leu	Thr Glu Leu Lys His Gly	Asp Gln Glu Ile Cys	Ala Gln Tyr		
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Trp Gly	Glu Gly Lys Gln Thr Tyr	Gly Asp Ile Glu Val	Asp Leu Lys		
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Asp Thr	Asp Lys Ser Ser Thr Tyr	Thr Leu Arg Val Phe	Glu Leu Arg		
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His Ser	Lys Arg Lys Asp Ser Arg	Thr Val Tyr Gln Tyr	Gln Tyr Thr		
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Leu Arg	Lys Ala Arg Pro Gly Met	Val Ser Thr Phe Glu	Gln Tyr Gln		
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Phe Leu	Tyr Asp Val Ile Ala Ser	Thr Tyr Pro Ala Gln	Asn Gly Gln		
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Val Lys	Lys Asn Asn His Gln Glu	Asp Lys Ile Glu Phe	Asp Asn Glu		
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Val Asp	Lys Val Lys Gln Asp Ala	Asn Cys Val Asn Pro	Leu Gly Ala		
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Pro Glu	Lys Leu Pro Glu Ala Lys	Glu Gln Ala Glu Gly	Ser Glu Pro		
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&lt;210&gt; 83

&lt;211&gt; 1291

&lt;212&gt; PRT

&lt;213&gt; Mus musculus

&lt;400&gt; 83

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Ser Thr Thr Glu Asn Ala Leu Leu Leu Pro Gln Ser Asp Pro Leu Pro
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Ala Arg Thr Thr Glu Ser Thr Pro Pro Ser Ile Ser Glu Arg Gly Asn
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Pro His Leu Ser Pro Gln Pro Asp Ser Gln Thr Pro Ser Ala Gly Gly
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          130          135          140
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Arg	Lys	Cys	Asn	Ser	Asp	Asn	Ile	Ser	Tyr	Val	Leu	His	Cys	Glu	Pro	305	310	315
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Gln	Thr	Asp	Leu	Gly	Ile	Pro	Glu	Thr	Pro	Lys	Pro	Ser	Cys	Gly	Asp	370	375	380
Pro	Ala	Ala	Arg	Lys	Thr	Leu	Val	Ser	Trp	Pro	Glu	Pro	Ala	Ser	Lys	385	390	395
Pro	Asp	Pro	Ala	Ser	Lys	Pro	His	Gly	Tyr	Val	Leu	Cys	Tyr	Lys	Asn	405	410	415
Asn	Ser	Glu	Lys	Cys	Lys	Ser	Leu	Pro	Asn	Asn	Val	Thr	Ser	Phe	Glu	420	425	430
Val	Glu	Ser	Leu	Lys	Pro	Tyr	Lys	Tyr	Tyr	Glu	Val	Ser	Leu	Leu	Ala	435	440	445
Tyr	Val	Asn	Gly	Lys	Ile	Gln	Arg	Asn	Gly	Thr	Ala	Glu	Lys	Cys	Asn	450	455	460
Phe	His	Thr	Lys	Ala	Asp	Arg	Pro	Asp	Lys	Val	Thr	Gly	Met	Lys	Thr	465	470	475
Ser	Arg	Pro	Thr	Asp	Asn	Ser	Ile	Asn	Val	Thr	Cys	Gly	Pro	Pro	Tyr	485	490	495
Glu	Thr	Asn	Gly	Pro	Lys	Thr	Phe	Tyr	Ile	Leu	Val	Val	Arg	Ser	Gly	500	505	510
Gly	Ser	Phe	Val	Thr	Lys	Tyr	Asn	Lys	Thr	Asn	Cys	Gln	Phe	Tyr	Val	515	520	525
Asp	Asn	Leu	Tyr	Tyr	Ser	Thr	Asp	Tyr	Glu	Phe	Leu	Val	Ser	Phe	His	530	535	540
Asn	Gly	Val	Tyr	Glu	Gly	Asp	Ser	Val	Ile	Arg	Asn	Glu	Ser	Thr	Asn	545	550	555
Phe	Asn	Ala	Lys	Ala	Leu	Ile	Ile	Phe	Leu	Val	Phe	Leu	Ile	Ile	Val	565	570	575
Thr	Ser	Ile	Ala	Leu	Leu	Val	Val	Leu	Tyr	Lys	Ile	Tyr	Asp	Leu	Arg	580	585	590
Lys	Lys	Arg	Ser	Ser	Asn	Leu	Asp	Glu	Gln	Gln	Glu	Leu	Val	Glu	Arg	595	600	605
Asp	Asp	Glu	Lys	Gln	Leu	Met	Asp	Val	Glu	Pro	Ile	His	Ser	Asp	Ile	610	615	620
Leu	Leu	Glu	Thr	Tyr	Lys	Arg	Lys	Ile	Ala	Asp	Glu	Gly	Arg	Leu	Phe	625	630	635
Leu	Ala	Glu	Phe	Gln	Ser	Ile	Pro	Arg	Val	Phe	Ser	Lys	Phe	Pro	Ile	645	650	655
Lys	Asp	Ala	Arg	Lys	Pro	His	Asn	Gln	Asn	Lys	Asn	Arg	Tyr	Val	Asp	660	665	670
Ile	Leu	Pro	Tyr	Asp	Tyr	Asn	Arg	Val	Glu	Leu	Ser	Glu	Ile	Asn	Gly	675	680	685
Asp	Ala	Gly	Ser	Thr	Tyr	Ile	Asn	Ala	Ser	Tyr	Ile	Asp	Gly	Phe	Lys	690	695	700
Glu	Pro	Arg	Lys	Tyr	Ile	Ala	Ala	Gln	Gly	Pro	Arg	Asp	Glu	Thr	Val	705	710	715

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 Met Val Thr Arg Cys Glu Glu Gly Asn Arg Asn Lys Cys Ala Glu Tyr  
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 Trp Pro Ser Met Glu Glu Gly Thr Arg Ala Phe Lys Asp Ile Val Val  
 755 760 765  
 Thr Ile Asn Asp His Lys Arg Cys Pro Asp Tyr Ile Ile Gln Lys Leu  
 770 775 780  
 Asn Val Ala His Lys Lys Glu Lys Ala Thr Gly Arg Glu Val Thr His  
 785 790 795 800  
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 Ser Gly Pro Ile Val Val His Cys Ser Ala Gly Val Gly Arg Thr Gly  
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 Thr Tyr Ile Gly Ile Asp Ala Met Leu Glu Gly Leu Glu Ala Glu Gly  
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 865 870 875 880  
 Leu Met Val Gln Val Glu Ala Gln Tyr Ile Leu Ile His Gln Ala Leu  
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 Glu Leu Glu Met Ser Lys Glu Ser Glu Pro Glu Ser Asp Glu Ser Ser  
 980 985 990  
 Asp Asp Asp Ser Asp Ser Glu Glu Thr Ser Lys Tyr Ile Asn Ala Ser  
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 Glu Val Cys Ala Gln Tyr Trp Gly Glu Gly Lys Gln Thr Tyr Gly Asp  
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 Lys Ala Ser Pro Glu Gly Met Lys Tyr His Lys His Ala Ser Ile Leu  
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 Phe Asn Leu Leu Glu Ser Ala Glu Thr Glu Asp Val Val Asp Val Phe  
 1170 1175 1180

Gln Val Val Lys Ser Leu Arg Lys Ala Arg Pro Gly Val Val Cys Ser  
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 1235 1240 1245  
 Pro Asp Gly Pro Leu Asn Lys Ala Gln Glu Asp Ser Arg Gly Val Gly  
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 <211> 3541  
 <212> DNA  
 <213> Rattus norvegicus

<400> 84  
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 gacaaaaaac ctaagtgtga atatacggat tgtgaaaaag agttaaaaaa tctaccagaa 180  
 tgctcacaga aaaacgtcac tctctccaat ggctcatgta ctccagataa aattataaat 240  
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 gctaatacct caatttgttt ggagtggaaa ataaaaaaca aatttacctg cgacattcaa 360  
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&lt;210&gt; 85

&lt;211&gt; 962

&lt;212&gt; PRT

&lt;213&gt; Rattus norvegicus

&lt;400&gt; 85

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Leu Thr Val Arg Thr Asn Tyr Thr Cys Ala Ala Glu Val Leu Tyr Asn
             20             25             30
Asn Val Ile Leu Leu Lys Gln Asp Arg Arg Val Gln Thr Asp Phe Gly
             35             40             45
Thr Pro Glu Met Leu Pro His Val Gln Cys Lys Asn Ser Thr Asn Ser
             50             55             60
Thr Thr Leu Val Ser Trp Ala Glu Pro Ala Ser Lys His His Gly Tyr
             65             70             75             80
Ile Leu Cys Tyr Lys Lys Thr Pro Ser Glu Lys Cys Glu Asn Leu Ala
             85             90             95
Asn Asp Val Asn Ser Phe Glu Val Lys Asn Leu Arg Pro Tyr Thr Glu
             100            105            110
Tyr Thr Val Ser Leu Phe Ala Tyr Val Ile Gly Arg Val Gln Arg Asn
             115            120            125
Gly Pro Ala Lys Asp Cys Asn Phe Arg Thr Lys Ala Ala Arg Pro Gly
             130            135            140
Lys Val Asn Gly Met Lys Thr Ser Arg Ala Ser Asp Asn Ser Ile Asn
             145            150            155            160
Val Thr Cys Asn Ser Pro Tyr Glu Ile Asn Gly Pro Glu Ala Arg Tyr
             165            170            175
Ile Leu Glu Val Lys Ser Gly Gly Ser Leu Val Lys Thr Phe Asn Gln
             180            185            190
Ser Thr Cys Lys Phe Val Val Asp Asn Leu Tyr Tyr Ser Thr Asp Tyr
             195            200            205
Glu Phe Leu Val Tyr Phe Tyr Asn Gly Glu Tyr Leu Gly Asp Pro Glu

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210		215		220	
Ile Lys Pro Gln Ser Thr	Ser Tyr Asn Ser Lys	Ala Leu Ile Ile Phe			
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Leu Val Phe Leu Ile Ile	Val Thr Ser Ile Ala	Leu Leu Val Val Leu			
	245	250		255	
Tyr Lys Ile Tyr Asp Leu	Arg Lys Lys Arg Ser	Ser Ser Asn Leu Asp	Glu		
	260	265		270	
Gln Gln Glu Leu Val Glu	Arg Asp Glu Glu Lys	Gln Leu Ile Asn Val			
	275	280		285	
Asp Pro Ile His Ser Asp	Leu Leu Leu Glu Thr	Tyr Lys Arg Lys Ile			
	290	295		300	
Ala Asp Glu Gly Arg Leu	Phe Leu Ala Glu Phe	Gln Ser Ile Pro Arg			
305	310	315		320	
Val Phe Ser Lys Phe Pro	Ile Lys Asp Ala Arg	Lys Ser Gln Asn Gln			
	325	330		335	
Asn Lys Asn Arg Tyr Val	Asp Ile Leu Pro Tyr	Asp Tyr Asn Arg Val			
	340	345		350	
Glu Leu Ser Glu Ile Asn	Gly Asp Ala Gly Ser	Thr Tyr Ile Asn Ala			
	355	360		365	
Ser Tyr Ile Asp Gly Phe	Lys Glu Pro Arg Lys	Tyr Ile Ala Ala Gln			
	370	375		380	
Gly Pro Arg Asp Glu Thr	Val Asp Asp Phe Trp	Lys Met Ile Trp Glu			
385	390	395		400	
Gln Lys Ala Thr Val Ile	Val Met Val Thr Arg	Cys Glu Glu Gly Asn			
	405	410		415	
Arg Asn Lys Cys Ala Glu	Tyr Trp Pro Cys Met	Glu Glu Gly Thr Arg			
	420	425		430	
Thr Phe Arg Asp Val Val	Val Thr Ile Asn Asp	His Lys Arg Cys Pro			
	435	440		445	
Asp Tyr Ile Ile Gln Lys	Leu Ser Ile Ala His	Lys Lys Glu Lys Ala			
	450	455		460	
Thr Gly Arg Glu Val Thr	His Ile Gln Phe Thr	Ser Trp Pro Asp His			
465	470	475		480	
Gly Val Pro Glu Asp Pro	His Leu Leu Leu Lys	Leu Arg Arg Arg Val			
	485	490		495	
Asn Ala Phe Ser Asn Phe	Phe Ser Gly Pro Ile	Val Val His Cys Ser			
	500	505		510	
Ala Gly Val Gly Arg Thr	Gly Thr Tyr Ile Gly	Ile Asp Ala Met Leu			
	515	520		525	
Glu Ser Leu Glu Ala Glu	Gly Lys Val Asp Val	Tyr Gly Tyr Val Val			
	530	535		540	
Asn Leu Arg Arg Gln Arg	Cys Leu Met Val Gln	Val Glu Ala Gln Tyr			
545	550	555		560	
Ile Leu Ile His Gln Ala	Leu Val Glu Tyr Asn	Gln Phe Gly Glu Thr			
	565	570		575	
Glu Val Asn Leu Ser Glu	Leu His Ser Cys Leu	Gln Asn Leu Lys Lys			
	580	585		590	
Arg Asp Pro Pro Ser Asp	Pro Ser Pro Leu Glu	Ala Glu Tyr Gln Arg			
	595	600		605	
Leu Pro Ser Tyr Arg Ser	Trp Arg Thr Gln His	Ile Gly Asn Gln Glu			
	610	615		620	
Glu Asn Lys Lys Lys Asn	Arg Ser Ser Asn Val	Pro Tyr Asp Phe			
625	630	635		640	
Asn Arg Val Pro Leu Lys	His Glu Leu Glu Met	Ser Lys Glu Ser Glu			
	645	650		655	
Ala Glu Ser Asp Glu Ser	Ser Asp Glu Asp Ser	Asp Ser Glu Glu Thr			
	660	665		670	
Ser Lys Tyr Ile Asn Ala	Ser Phe Val Met Ser	Tyr Trp Lys Pro Glu			

675	680	685
Met Met Ile Ala Ala Gln Gly Pro Leu Lys Glu Thr Ile Gly Asp Phe		
690	695	700
Trp Gln Met Ile Phe Gln Arg Lys Val Lys Val Ile Val Met Leu Thr		
705	710	715
Glu Leu Met Ser Gly Asp Gln Glu Val Cys Ala Gln Tyr Trp Gly Glu		
725	730	735
Gly Lys Gln Thr Tyr Gly Asp Met Glu Val Met Leu Lys Asp Thr Asn		
740	745	750
Lys Ser Ser Ala Tyr Ile Leu Arg Ala Phe Glu Leu Arg His Ser Lys		
755	760	765
Arg Lys Glu Pro Arg Thr Val Tyr Gln Tyr Gln Cys Thr Thr Trp Lys		
770	775	780
Gly Glu Glu Leu Pro Ala Glu Pro Lys Asp Leu Val Thr Leu Ile Gln		
785	790	795
Asn Ile Lys Gln Lys Leu Pro Lys Ser Gly Ser Glu Gly Met Lys Tyr		
805	810	815
His Lys His Ala Ser Ile Leu Val His Cys Arg Asp Gly Ser Gln Gln		
820	825	830
Thr Gly Leu Phe Cys Ala Leu Phe Asn Leu Leu Glu Ser Ala Glu Thr		
835	840	845
Glu Asp Val Val Asp Val Phe Gln Val Val Lys Ser Leu Arg Lys Ala		
850	855	860
Arg Pro Gly Met Val Gly Ser Phe Glu Gln Tyr Gln Phe Leu Tyr Asp		
865	870	875
Ile Met Ala Ser Ile Tyr Pro Thr Gln Asn Gly Gln Val Lys Lys Ala		
885	890	895
Asn Ser Gln Asp Lys Ile Glu Phe His Asn Glu Val Asp Gly Ala Lys		
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Gln Asp Ala Asn Cys Val Gln Pro Ala Asp Pro Leu Asn Lys Ala Gln		
915	920	925
Glu Asp Ser Lys Glu Val Gly Ala Ser Glu Pro Ala Ser Gly Ser Glu		
930	935	940
Glu Pro Glu His Ser Ala Asn Gly Pro Met Ser Pro Ala Leu Thr Pro		
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Ser Ser		960

&lt;210&gt; 86

&lt;211&gt; 2090

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; 2090

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 86

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 <211> 595  
 <212> PRT  
 <213> Homo sapiens

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 Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp Leu Tyr  
 50 55 60  
 Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr Tyr Thr  
 65 70 75 80  
 Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile His Leu  
 85 90 95  
 Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp Tyr His  
 100 105 110  
 Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala Lys Gly  
 115 120 125  
 Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro Gly Asp  
 130 135 140  
 Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro Gly Ser  
 145 150 155 160  
 Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly Arg Tyr  
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 Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu Val Glu  
 180 185 190

His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe Val Tyr  
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 210 215 220  
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&lt;210&gt; 88

&lt;211&gt; 2277

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 88

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&lt;210&gt; 89

&lt;211&gt; 597

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 89

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Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp
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Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr
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Tyr Thr Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile

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111

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 <212> DNA  
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<210> 91  
 <211> 595  
 <212> PRT  
 <213> Homo sapiens

<400> 91

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Arg	Lys	Asn	Gln	Gly	Asp	Phe	Ser	Leu	Ser	Val	Arg	Val	Gly	Asp	Gln
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Val	Thr	His	Ile	Arg	Ile	Gln	Asn	Ser	Gly	Asp	Phe	Tyr	Asp	Leu	Tyr
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Lys	Tyr	Pro	Leu	Asn	Cys	Ser	Asp	Pro	Thr	Ser	Glu	Arg	Trp	Tyr	His
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Phe	Val	Leu	Ser	Val	Leu	Ser	Asp	Gln	Pro	Lys	Ala	Gly	Pro	Gly	Ser
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His	Phe	Lys	Lys	Thr	Gly	Ile	Glu	Glu	Ala	Ser	Gly	Ala	Phe	Val	Tyr
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Tyr	Ile	Ala	Ser	Gln	Gly	Cys	Leu	Glu	Ala	Thr	Val	Asn	Asp	Phe	Trp
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Gln	Met	Ala	Trp	Gln	Glu	Asn	Ser	Arg	Val	Ile	Val	Met	Thr	Thr	Arg
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Trp	Pro	Asp	His	Gly	Val	Pro	Ser	Glu	Pro	Gly	Gly	Val	Leu	Ser	Phe
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&lt;210&gt; 92

&lt;211&gt; 4301

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

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&lt;222&gt; 387, 388, 3718, 3799, 4224

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 92

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			100					105					110		
Phe	Trp	Arg	Met	Ile	Trp	Glu	Tyr	Arg	Ile	Leu	Val	Ile	Val	Met	Ala
		115					120						125		
Cys	Met	Glu	Phe	Glu	Met	Gly	Lys	Lys	Lys	Cys	Glu	Arg	Tyr	Trp	Ala
		130				135					140				
Glu	Pro	Gly	Glu	Thr	Gln	Leu	Gln	Phe	Gly	Pro	Phe	Ser	Ile	Ser	Cys
145					150					155				160	
Glu	Ala	Glu	Lys	Lys	Lys	Ser	Asp	Tyr	Lys	Ile	Arg	Thr	Leu	Lys	Ala
			165						170					175	
Lys	Phe	Asn	Asn	Glu	Thr	Arg	Ile	Ile	Tyr	Gln	Phe	His	Tyr	Lys	Asn
		180						185					190		
Trp	Pro	Asp	His	Asp	Val	Pro	Ser	Ser	Ile	Asp	Pro	Ile	Leu	Gln	Leu
		195					200					205			
Ile	Trp	Asp	Met	Arg	Cys	Tyr	Gln	Glu	Asp	Asp	Cys	Val	Pro	Ile	Cys
		210				215					220				

Ile	His	Cys	Ser	Ala	Gly	Cys	Gly	Arg	Thr	Gly	Val	Ile	Cys	Ala	Val
225					230					235					240
Asp	Tyr	Thr	Trp	Met	Leu	Leu	Lys	Asp	Gly	Ile	Ile	Pro	Lys	Asn	Phe
				245					250					255	
Ser	Val	Phe	Asn	Leu	Ile	Gln	Glu	Met	Arg	Thr	Gln	Arg	Pro	Ser	Leu
			260					265					270		
Val	Gln	Thr	Gln	Glu	Gln	Tyr	Glu	Leu	Val	Tyr	Ser	Ala	Val	Leu	Glu
		275					280					285			
Leu	Phe	Lys	Arg	His	Met	Asp	Val	Ile	Ser	Asp	Asn	His	Leu	Gly	Arg
	290					295					300				
Glu	Ile	Gln	Ala	Gln	Cys	Ser	Ile	Pro	Glu	Gln	Ser	Leu	Thr	Val	Glu
305					310					315					320
Ala	Asp	Ser	Cys	Pro	Leu	Asp	Leu	Pro	Lys	Asn	Ala	Met	Arg	Asp	Val
				325					330					335	
Lys	Thr	Thr	Asn	Gln	His	Ser	Lys	Gln	Gly	Ala	Glu	Ala	Glu	Ser	Thr
			340					345					350		
Gly	Gly	Ser	Ser	Leu	Gly	Leu	Arg	Thr	Ser	Thr	Met	Asn	Ala	Glu	Glu
		355					360					365			
Glu	Leu	Val	Leu	His	Ser	Ala	Lys	Ser	Ser	Pro	Ser	Phe	Asn	Cys	Leu
	370					375					380				
Glu	Leu	Asn	Cys	Gly	Cys	Asn	Asn	Lys	Ala	Val	Ile	Thr	Arg	Asn	Gly
385					390					395					400
Gln	Ala	Arg	Ala	Ser	Pro	Val	Val	Gly	Glu	Pro	Leu	Gln	Lys	Tyr	Gln
				405					410					415	
Ser	Leu	Asp	Phe	Gly	Ser	Met	Leu	Phe	Gly	Ser	Cys	Pro	Ser	Ala	Leu
		420						425					430		
Pro	Ile	Asn	Thr	Ala	Asp	Arg	Tyr	His	Asn	Ser	Lys	Gly	Pro	Val	Lys
	435						440					445			
Arg	Thr	Lys	Ser	Thr	Pro	Phe	Glu	Leu	Ile	Gln	Gln	Arg	Lys	Thr	Asn
	450					455					460				
Asp	Leu	Ala	Val	Gly	Asp	Gly	Phe	Ser	Cys	Leu	Glu	Ser	Gln	Leu	His
465					470					475					480
Glu	His	Tyr	Ser	Leu	Arg	Glu	Leu	Gln	Val	Gln	Arg	Val	Ala	His	Val
				485					490					495	
Ser	Ser	Glu	Glu	Leu	Asn	Tyr	Ser	Leu	Pro	Gly	Ala	Cys	Asp	Ala	Ser
				500				505					510		
Cys	Val	Pro	Arg	His	Ser	Pro	Gly	Ala	Leu	Arg	Val	His	Leu	Tyr	Thr
		515					520					525			
Ser	Leu	Ala	Glu	Asp	Pro	Tyr	Phe	Ser	Ser	Ser	Pro	Pro	Asn	Ser	Ala
	530					535					540				
Asp	Ser	Lys	Met	Ser	Phe	Asp	Leu	Pro	Glu	Lys	Gln	Asp	Gly	Ala	Thr
545					550					555					560
Ser	Pro	Gly	Ala	Leu	Pro	Ala	Ser	Ser	Thr	Thr	Ser	Phe	Phe	Thr	
				565					570					575	
Ser	Asn	Pro	His	Asp	Ser	Leu	Val	Met	Asn	Thr	Leu	Thr	Ser	Phe	Ser
				580				585					590		
Pro	Pro	Leu	Asn	Gln	Glu	Thr	Ala	Val	Glu	Ala	Pro	Ser	Arg	Arg	Thr
		595					600					605			
Asp	Asp	Glu	Ile	Pro	Pro	Pro	Leu	Pro	Glu	Arg	Thr	Pro	Glu	Ser	Phe
	610					615					620				
Ile	Val	Val	Glu	Glu	Ala	Gly	Glu	Pro	Ser	Pro	Arg	Val	Thr	Glu	Ser
625					630					635					640
Leu	Pro	Leu	Val	Val	Thr	Phe	Gly	Ala	Ser	Pro	Glu	Cys	Ser	Gly	Thr
				645				650						655	
Ser	Glu	Met	Lys	Ser	His	Asp	Ser	Val	Gly	Phe	Thr	Pro	Ser	Lys	Asn
			660					665					670		
Val	Lys	Leu	Arg	Ser	Pro	Lys	Ser	Asp	Arg	His	Gln	Asp	Gly	Ser	Pro
		675					680					685			

Pro Pro Pro Leu Pro Glu Arg Thr Leu Glu Ser Phe Phe Leu Ala Asp  
 690 695 700  
 Glu Asp Cys Ile Gln Ala Gln Ala Val Gln Thr Ser Ser Thr Ser Tyr  
 705 710 715 720  
 Pro Glu Thr Thr Glu Asn Ser Thr Ser Ser Lys Gln Thr Leu Arg Thr  
 725 730 735  
 Pro Gly Lys Ser Phe Thr Arg Ser Lys Ser Leu Lys Ile Phe Arg Asn  
 740 745 750  
 Met Lys Lys Ser Val Cys Asn Ser Ser Ser Pro Ser Lys Pro Thr Glu  
 755 760 765  
 Arg Val Gln Pro Lys Asn Ser Ser Ser Phe Leu Asn Phe Gly Phe Gly  
 770 775 780  
 Asn Arg Phe Ser Lys Pro Lys Gly Pro Arg Asn Pro Pro Ser Ala Trp  
 785 790 795 800  
 Asn Met

&lt;210&gt; 96

&lt;211&gt; 2176

&lt;212&gt; DNA

<213> *Rattus norvegicus*

&lt;400&gt; 96

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 ctcgattggc cccgcccttg tcgccctttg cctgtgactt cccccactcc tccagggaga 180  
 tgcgtgcccg cgggtgggtt caccgggacc tcagtgggcc tgatgccgag accctgctca 240  
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 ctgattacat caatgccaac tacgttaaga accagctgct aggtccggat gagaactcta 1140  
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 cactggacaa tggggacctg gttcgggaga tatggcacta ccagtacctg agctggcctg 1440  
 accatggggt tcccagtgag cctggagggt tcctcagctt tctggatcag atcaaccagc 1500  
 ggcaggaaaag tttgcctcac gcggggccca tcattgtgca ttgcagcgct ggcacggccc 1560  
 gcaccggcac catcatcgtc attgatatgc tcatggagag cgtctccacc aaggggctag 1620  
 actgtgacat tgacatccag aagaccatcc agatggtacg ggcacagcgc tctggcatgg 1680  
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 tcacctaccc tccggctttg aggagtcccc acgcccgaagc ctcccgtacc tcgtccaaac 1860  
 acaaggagga ggtgtacgaa aacgtgcata gcaagaacaa gaaggaagag aaagtaaaga 1920  
 agcagcgatc ggcagacaag gagaagaaca aaggttctct caagaggaac atcagcctta 1980  
 ctccgtgcag aggcctccgc tgggcagaca gagacctgta gtccacacca ccccatctt 2040



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gttgtaattt aagtgaccgt ggtcctctga acctgtatat ggctcagcaa gcctcagggg 2100
gagtcagacc cttctcttct tgtaaataaa gcccctggac aactgtgtaa aaaaaaaaaa 2160
aaaaaaaaaa ctcgag                                     2176

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&lt;210&gt; 97

&lt;211&gt; 613

&lt;212&gt; PRT

&lt;213&gt; Rattus norvegicus

&lt;400&gt; 97

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Met Leu Ser Arg Gly Trp Phe His Arg Asp Leu Ser Gly Pro Asp Ala
 1          5          10          15
Glu Thr Leu Leu Lys Gly Arg Gly Val Pro Gly Ser Phe Leu Ala Arg
 20          25          30
Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Asp
 35          40          45
Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp
 50          55          60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Ser Thr Glu Leu Val Glu Tyr
 65          70          75          80
Tyr Thr Gln Gln Gln Gly Ile Leu Gln Asp Arg Asp Gly Thr Ile Ile
 85          90          95
His Leu Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp
100          105          110
Tyr His Gly His Met Ser Gly Gly Gln Ala Glu Ser Leu Leu Gln Ala
115          120          125
Lys Gly Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro
130          135          140
Gly Asp Phe Val Leu Ser Val Leu Asn Asp Gln Pro Lys Ala Ala Pro
145          150          155          160
Gly Ser Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly
165          170          175
Arg Tyr Thr Val Gly Gly Ser Glu Thr Phe Asp Ser Leu Thr Asp Leu
180          185          190
Val Glu His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe
195          200          205
Val Tyr Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp
210          215          220
Ile Glu Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp
225          230          235          240
Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln
245          250          255
Glu Ala Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn
260          265          270
Lys Ser Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg
275          280          285
Val Ile Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile
290          295          300
Asn Ala Asn Tyr Val Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ser
305          310          315          320
Lys Thr Tyr Ile Ala Ser Gln Gly Cys Leu Asp Ala Thr Val Asn Asp
325          330          335
Phe Trp Gln Met Ala Trp Gln Glu Asn Thr Arg Val Ile Val Met Thr
340          345          350
Thr Arg Glu Val Glu Lys Gly Arg Asn Lys Cys Val Pro Tyr Trp Pro
355          360          365
Glu Val Gly Thr Gln Arg Val Tyr Gly Leu Tyr Ser Val Thr Asn Cys
370          375          380

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Lys Glu His Asp Thr Ala Glu Tyr Lys Leu Arg Thr Leu Gln Ile Ser
385                      390                      395                      400
Pro Leu Asp Asn Gly Asp Leu Val Arg Glu Ile Trp His Tyr Gln Tyr
                      405                      410                      415
Leu Ser Trp Pro Asp His Gly Val Pro Ser Glu Pro Gly Gly Val Leu
                      420                      425                      430
Ser Phe Leu Asp Gln Ile Asn Gln Arg Gln Glu Ser Leu Pro His Ala
                      435                      440                      445
Gly Pro Ile Ile Val His Cys Ser Ala Gly Ile Gly Arg Thr Gly Thr
                      450                      455                      460
Ile Ile Val Ile Asp Met Leu Met Glu Ser Val Ser Thr Lys Gly Leu
465                      470                      475                      480
Asp Cys Asp Ile Asp Ile Gln Lys Thr Ile Gln Met Val Arg Ala Gln
                      485                      490                      495
Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Lys Phe Ile Tyr Val
                      500                      505                      510
Ala Ile Ala Gln Phe Ile Glu Thr Thr Lys Lys Lys Leu Glu Ile Ile
                      515                      520                      525
Gln Ser Gln Arg Gly Gln Glu Ser Glu Tyr Gly Asn Ile Thr Tyr Pro
                      530                      535                      540
Pro Ala Leu Arg Ser Ala His Ala Lys Ala Ser Arg Thr Ser Ser Lys
545                      550                      555                      560
His Lys Glu Glu Val Tyr Glu Asn Val His Ser Lys Asn Lys Lys Glu
                      565                      570                      575
Glu Lys Val Lys Lys Gln Arg Ser Ala Asp Lys Glu Lys Asn Lys Gly
                      580                      585                      590
Ser Leu Lys Arg Asn Ile Ser Leu Thr Pro Cys Arg Gly Leu Arg Trp
                      595                      600                      605
Ala Asp Arg Asp Leu
610

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<210> 98  
 <211> 11  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Unique signature sequence motif found within  
 conserved domain

<221> VARIANT  
 <222> 1  
 <223> Xaa = Ile or Val

<221> VARIANT  
 <222> 4, 7, 8  
 <223> Xaa = Any Amino Acid

<221> VARIANT  
 <222> 10  
 <223> Xaa = Ser or Thr

<400> 98  
 Xaa His Cys Xaa Ala Gly Xaa Xaa Arg Xaa Gly  
 1 5 10